



# ANNALS of SURGERY

A MONTHLY REVIEW OF SURGICAL SCIENCE AND PRACTICE

*Also the Official Publication of the American Surgical Association,  
the Southern Surgical Association, Philadelphia Academy of  
Surgery, and New York Surgical Society*



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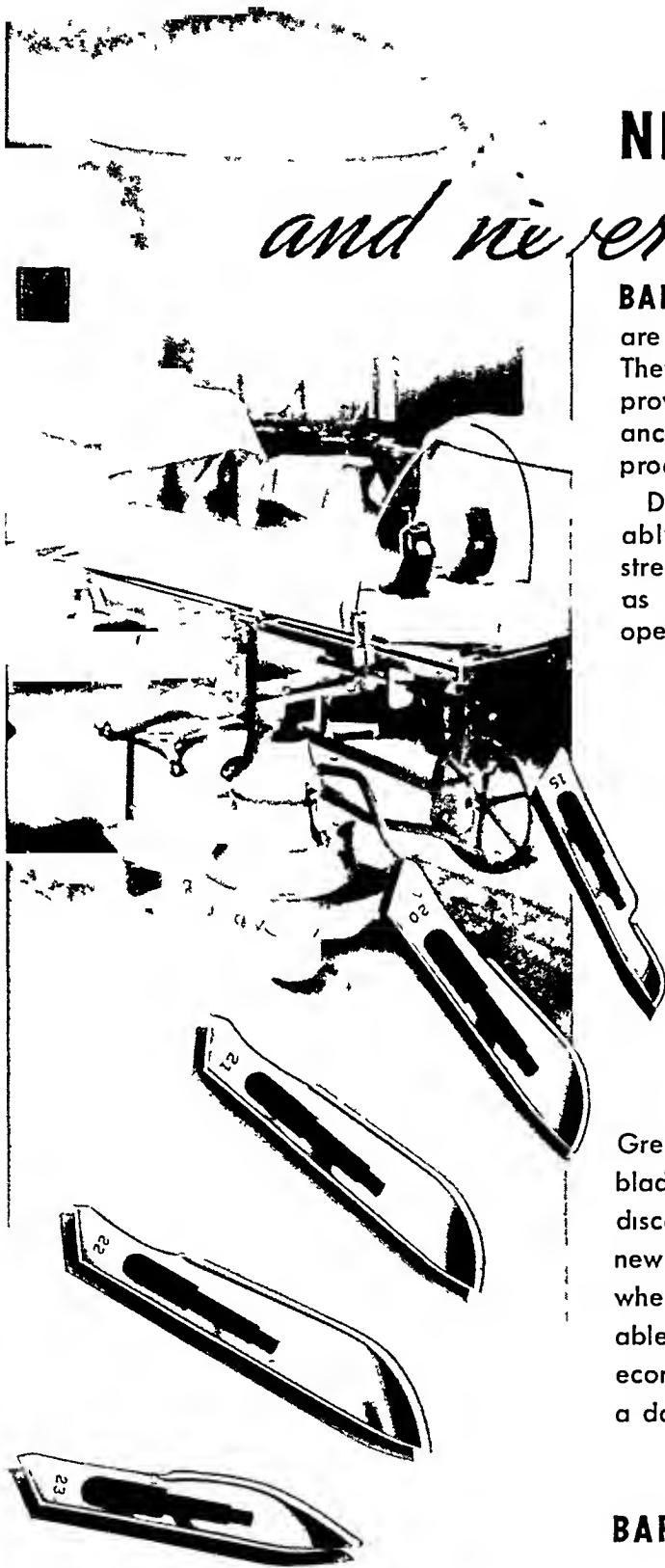
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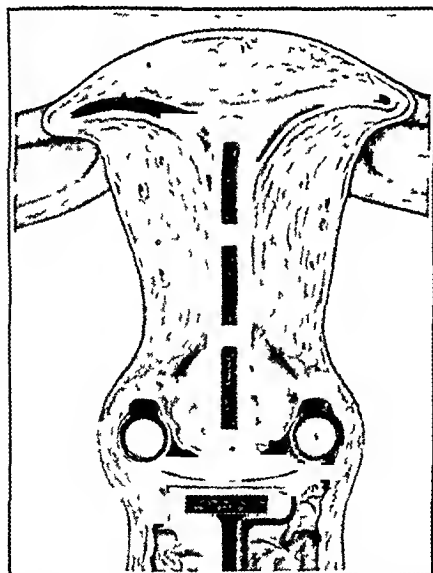
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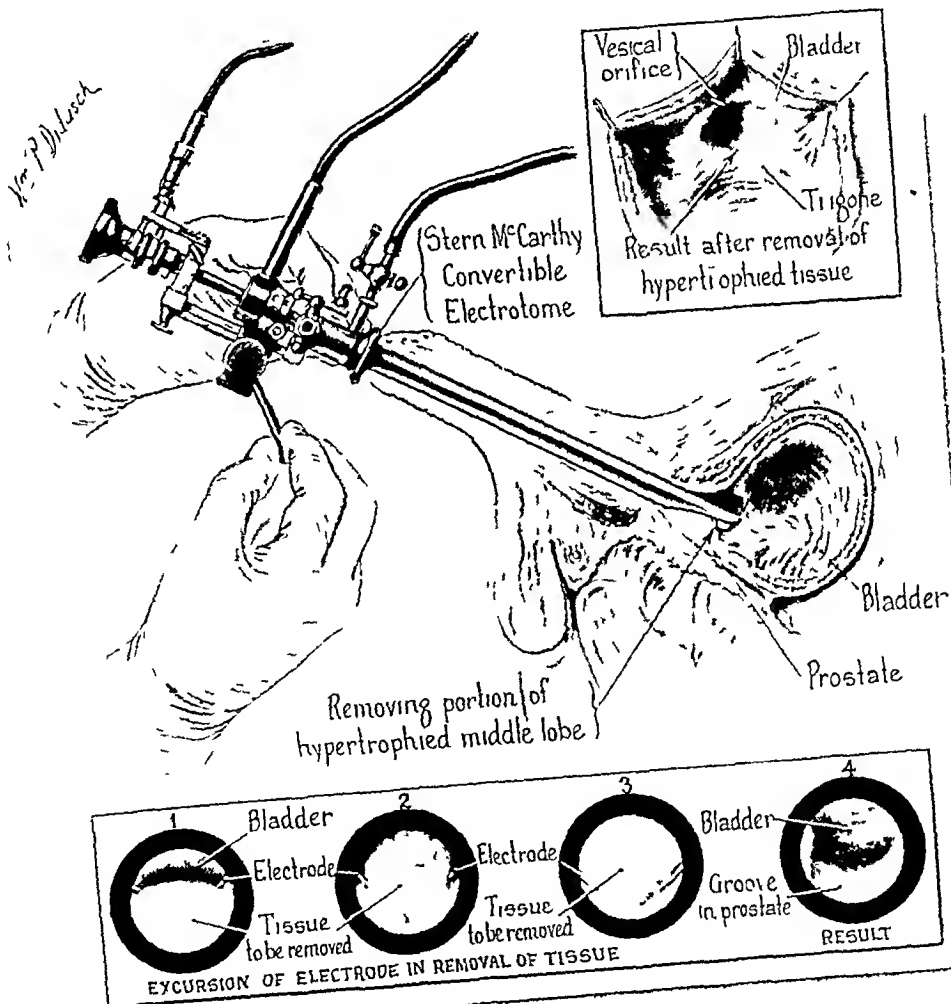
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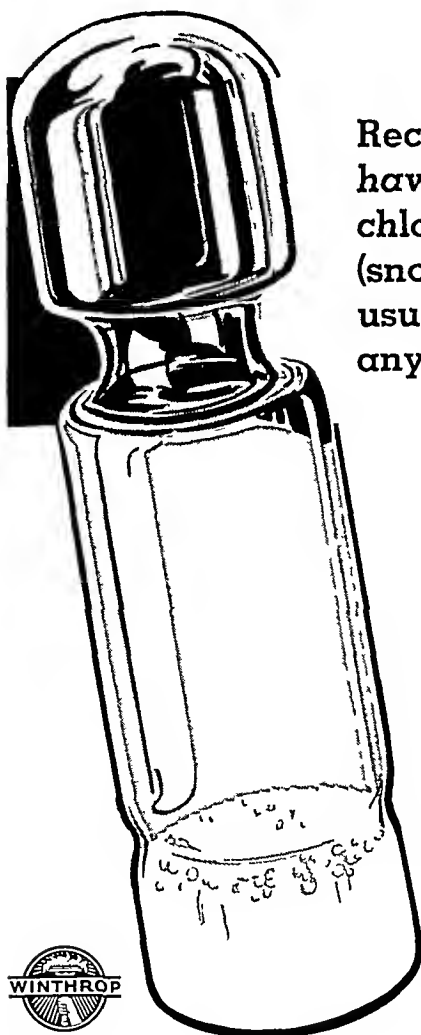
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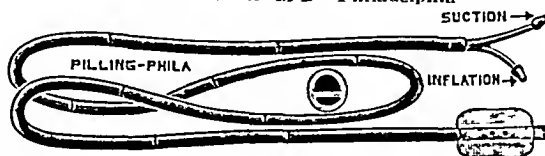
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*(See American Journal of Medical Sciences 187 595 1934 and  
Surgery Gynecology and Obstetrics page 692 April 1933)*

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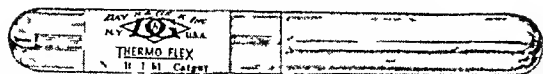
tures lethal to the most resistant organisms and spores — is applied AFTER the sutures are hermetically sealed in glass tubes and are thus protected.

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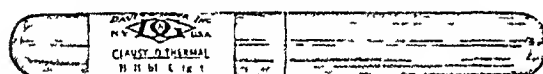


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1485	40-Day Chromic	" 5'

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Package of 12 tubes of a kind \$3 60

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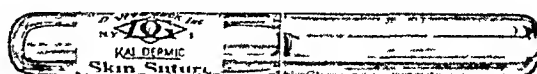


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NO		LENGTH
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1225	10-Day Chromic	" 5'
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Sizes 8-0 6-0 4-0 000 00 0

In packages of 12 tubes of a kind and size

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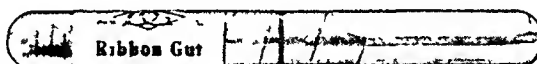
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855	Without Needle 20"	1 80

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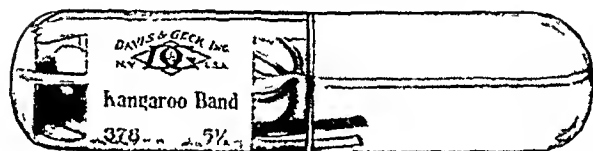
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360	Horsehair	168"	00
390	White Silk worm Gut	84"	00, 0, 1
400	Black Silk worm Gut	84"	00, 0, 1
450	White Twisted Silk	60"	000 to 3
460	Black Twisted Silk	60"	000, 0, 2
480	White Braided Silk	60"	00, 0, 2, 4
490	Black Braided Silk	60"	00, 1, 4

BOILABLE

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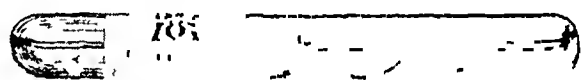
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900	Assorted Catgut, Silk, and Kal-dermic		



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NO		LENGTH	SIZES
903	Plain Catgut	20"	00 to 2
923	20-Day Chromic Catgut	20"	00 to 2
953	Kal-dermic	20"	000, 00, 0
963	Horsehair	two 28" strands	00
973	White Silk worm Gut	two 14" strands	0
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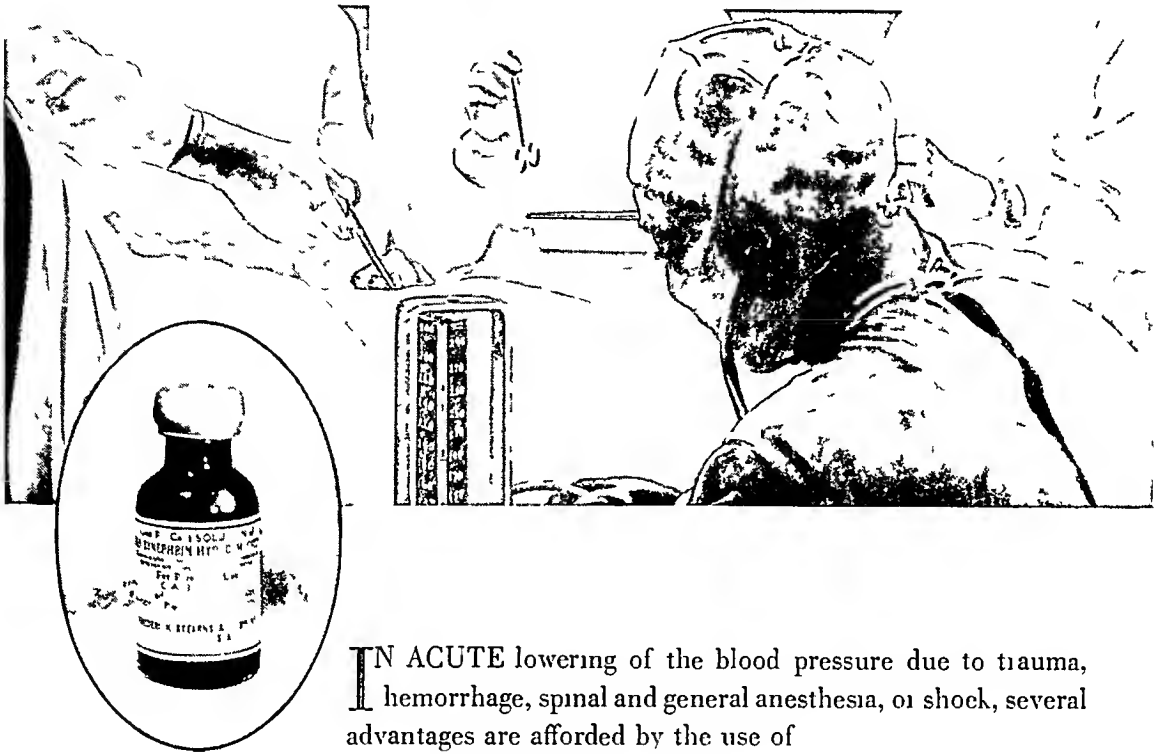
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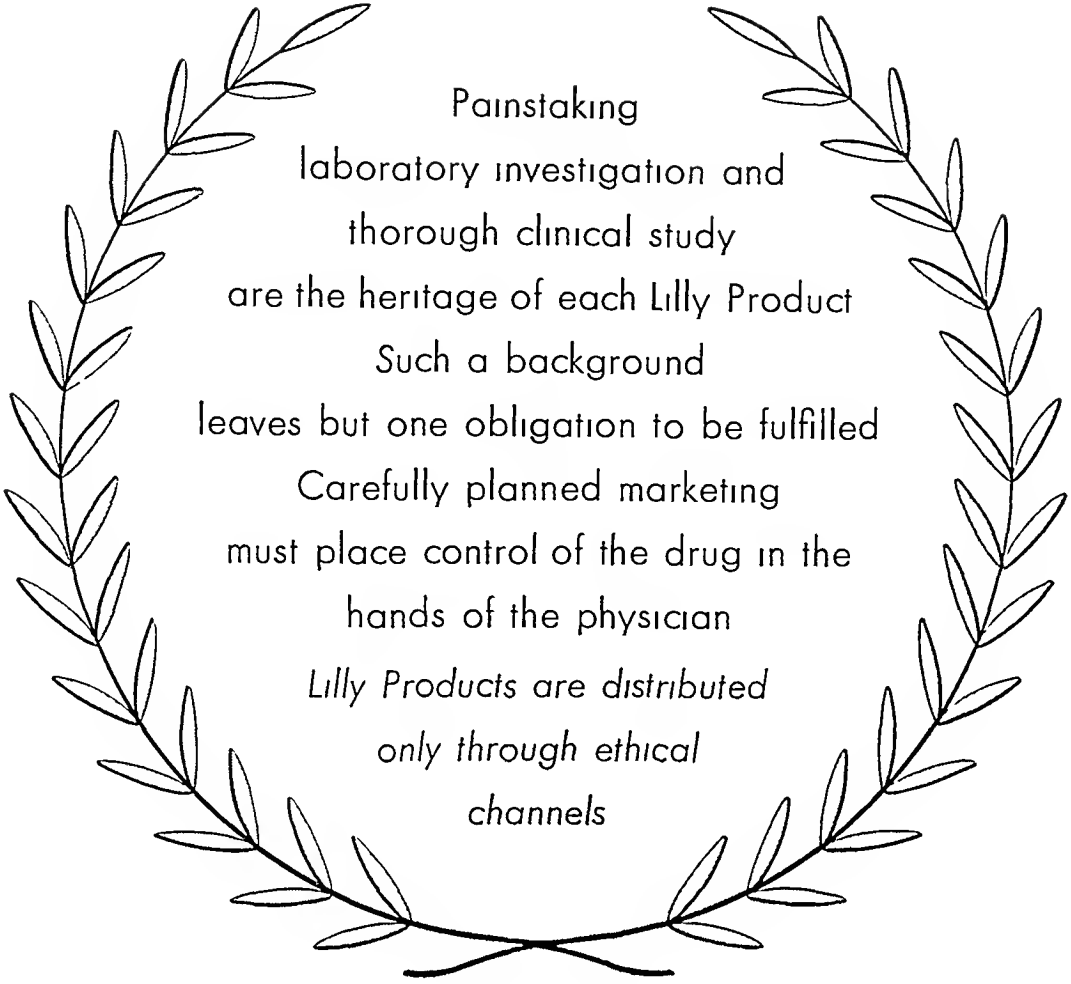
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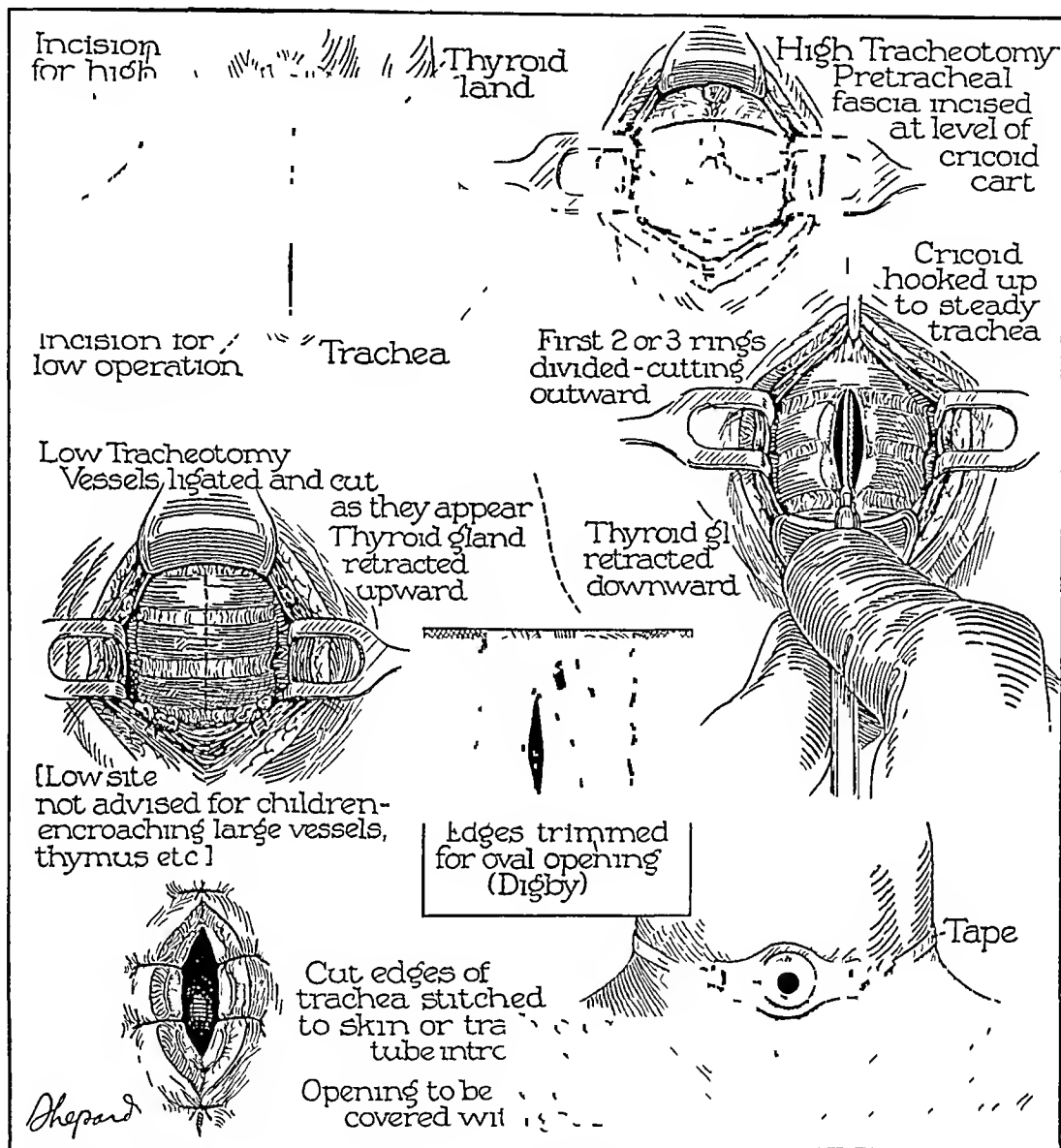
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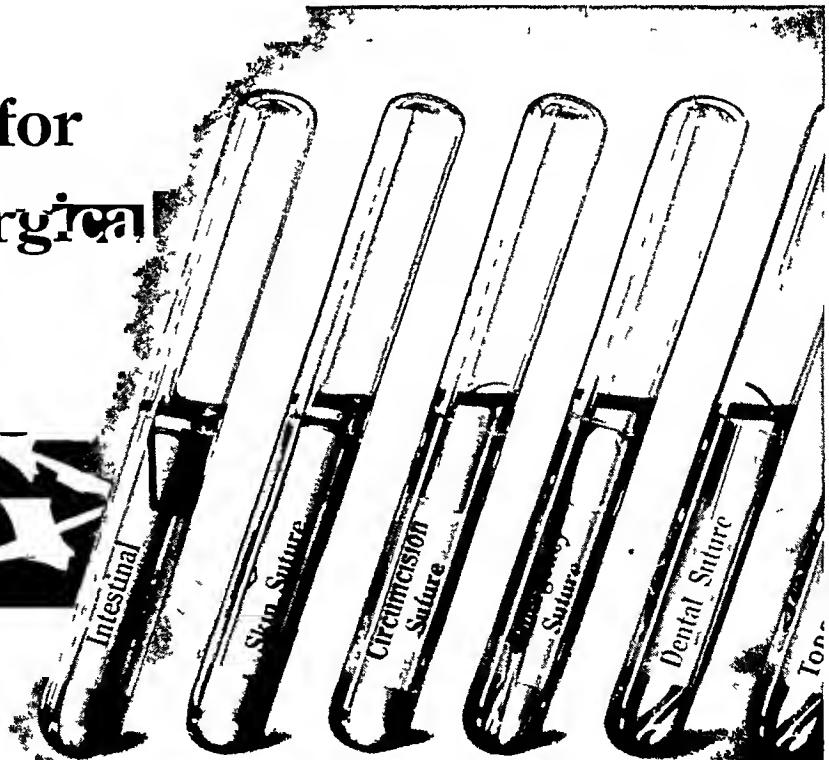
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# ANNALS OF SURGERY

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## LIGATURE OF THE COMMON CAROTID ARTERY IN CANCER OF THE HEAD AND NECK\*

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DR. JAMES R. WOOD,<sup>43</sup> in 1857, stated that "Ligature of the common carotid artery is justly considered a most important surgical operation. Although, ordinarily, not difficult of execution, yet, the consequences which are liable to follow the complete and permanent obstruction of one of the two vessels which supply the brain with the greatest share of its blood, will always render this operation a subject of grave consideration before its execution. Cerebral softening, with its concomitant symptoms, secondary hemorrhage, *etc*, are complications of the original disease for which ligature of the carotid may have been undertaken, which no prudent surgeon will heedlessly encounter."

Great importance was attached to the operation by surgeons of this early period due to the variety of diseases and accidents for which it was undertaken. Patients with such common ailments as headache, neuralgia, epilepsy, and aortic aneurysm were considered suitable subjects for this operation regardless of its appallingly high mortality rate. The propriety of such operations was questioned by the more conservative surgeons, but the procedure became more and more popular up to the turn of the present century. Recently, few pertinent reports have appeared in the literature. The procedure is now much less common and the indications for its use are more limited. Improved technic has markedly reduced the postoperative mortality in uncomplicated cases, but, as Doctor Wood foresaw, the operation continues to be a serious one, which requires grave consideration before its execution.

Before discussing the present series of 20 cases, in which ligation of the common carotid became necessary, it might be interesting to examine briefly into the history of the operation itself. We know that the art of ligature for hemorrhage was known to the ancients, and Garrison<sup>20</sup> states that "Helio-

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\* Read before the Surgical Section, New York Academy of Medicine, January 7, 1938.  
Submitted for publication March 29, 1938.

dorus, who antedated Celsus, gave the first account of ligation and torsion of blood vessels" The common carotid artery, which, due to its exposed location, could be easily lacerated in primitive hand to hand warfare, was quite possibly often ligated in a heroic attempt to control hemorrhage However, no authentic accounts of such operations are available to us

The fifteenth century is notable for many achievements, including the popularization of the use of gunpowder and the development of the art of printing It is significant that at this time, nearly 16 centuries after Heliodorus, we find the indications for and methods of application of the ligature again discussed, this time by Leonardo Pertopaglia, a professor at Padua

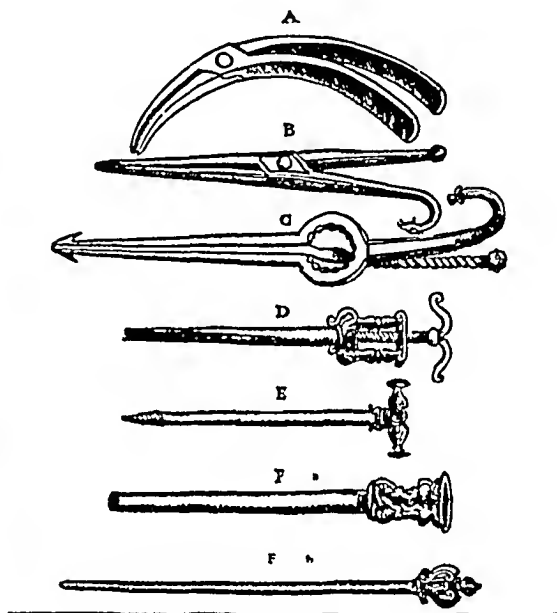


FIG 1—Ambroise Pare at the age of 45, and some of his surgical instruments (A) The *Bec de Corbin* with which he grasped a bleeding vessel in order to ligate it (from Harvey's History of Hemostasis)

About the year 1552, Ambroise Pare<sup>33</sup> is reported by deFourmestrau<sup>13</sup> to have been called upon to attend a patient, François Prevost, who had been wounded in a duel An *epee* cut across the neck had caused a severe laceration of the internal jugular vein and the common carotid artery of the left side The resulting loss of blood was great After considerable difficulty the flow of blood was arrested and the patient's life spared, but he developed a left monoplegia and aphasia

It is known that Pare, in performing his war-wound amputations at this time, was employing a crude type of bullet-grasping forceps (*Bec de Corbin* [Fig 1]) to clamp bleeding vessels, as well as ligatures with which to tie the vessels cut through We have no definite proof that this technic was used in the above case Nevertheless, his case report stands as the first published account in which the common carotid artery was operatively occluded

in man His artery-grasping forceps were probably the first instruments used for this purpose, and so are properly called the forerunners of the modern hemostat

Hebenstreit,<sup>21</sup> in a German translation of Bell's Surgery, mentions a case in which the common carotid artery was wounded in the extirpation of a scirrhus tumor, and the surgeon immediately applied a ligature and arrested the hemorrhage Most authorities regard this as one of the earliest recorded cases of ligation of the common carotid artery, but unfortunately no dates are given

In the history of this operation, the early sources are as obscure and indefinite as the following report by Averill,<sup>2</sup> in 1823 "Dr Cheston, of Gloucester, used to mention that Mr Warner of Guy's Hospital in removing a glandular tumor from the neck wounded the carotid artery and that the flow of blood was so profuse the patient fell back and fainted, when Mr Else instantly passed a ligature and secured the vessel, this happened nearly fifty years ago" The date of that operation would, therefore, be about 1775

Abernethy<sup>3</sup> reports the case of a man who was gored in the neck by a cow The horn entered by the left side of the cricoid cartilage and penetrated to the cervical vertebrae, passed upward and emerged behind the angle of the jaw To control hemorrhage, the common carotid artery was cautiously ligated Mr Abernethy first gradually tightened the ligature and then relaxed it, and as no cerebral symptoms occurred and the bleeding stopped, he tied the ligature firmly Convulsions supervened and death took place 30 hours after the operation Again no date is given, but it is supposed that this operation was performed about 1778-1779

In the London Lancet, October 6, 1832, there is a report of a clinical lecture delivered in Westminster Hospital by a Mr Lynn who had been assistant to John Hunter for many years Mr Lynn stated that 40 years ago he had been forced to ligate a common carotid artery because of late post-operative hemorrhage following the extirpation of a parotid gland The hemorrhage stopped immediately "The patient lived a fortnight and then died, evidently of the debility induced by the hemorrhage and her previous suffering" Mr Lynn believed this to be the first instance of ligation of the carotid According to his statement the operation must have been performed about 1792

The first authentic and completely reported operation for common carotid artery ligation took place on board His Majesty's Ship *Tonnant*, October 17, 1803 A servant had attempted suicide by slashing his throat The hemorrhage was stopped by the ship's surgeon, Mr Fleming, who, though he had never heard of a similar operation, placed a ligature around the carotid and tied it The patient recovered The case was reported in detail in the Medical Chirurgical Journal for January, 1817, long after the death of the operator, by a Doctor Coley<sup>10</sup> who had been assistant to Mr Fleming

The second authentic operation for common carotid ligation took place 18 days later The operator was Doctor Cogswell<sup>6</sup> of Hartford Connecticut This was the first case to be operated upon in this country and also the first

definitely recorded instance in which the ligation became necessary during the extirpation of a neck tumor. The patient made a good postoperative recovery but died of hemorrhage on the twentieth day.

Astley Cooper<sup>7</sup> performed the first common carotid artery ligation for aneurysm of that artery, November 1, 1805. On the eighth postoperative day, the patient developed a hemiplegia, and died on the twenty-first day.

Later, the procedure became a familiar one to many surgeons both here and abroad. The operation became popular and was performed in the attempted relief of primary head, neck and brain tumors, headache, epilepsy, neuralgia, hemiplegia, loss of vision, exophthalmos, hemorrhage from the nose and telangiectasis of the cheek. One hundred years of surgical experience were necessary before this operation and its indications and dangers were well established. To-day it is performed most frequently for injuries, for pulsating exophthalmos, and in the course of the surgical extirpation of neoplasms of the cervical region. It is also recommended in cases of cavernous sinus thrombosis (Eagleton<sup>16</sup>). Such authors as Wood<sup>43</sup> and Wyeth<sup>45</sup> have collected from the literature on the subject large numbers of cases of common carotid ligation, which were performed for many different primary diseases. From these collected data unsound conclusions were drawn as to the value and dangers of the procedure. In this report, it is our plan to discuss 20 cases in which it became necessary to ligate the common carotid artery either as a measure to control actual or threatened hemorrhage, 14 cases, or as an acute necessity during an operative procedure for the removal of a cervical tumor, six cases (Table I).

The first case in this group was operated upon, March 3, 1926, and the most recent case, December 10, 1937. It is apparent from the fact that an operation performed only 20 times in 11 years on an active head and neck tumor service, that the procedure is a rare one and that emergencies warranting its employment do not arise frequently. These cases indicate the seriousness of the operation for common carotid ligation when such becomes necessary in the treatment of cancer patients, either for the control of hemorrhage or at an operation for the removal of a large cervical tumor. A clear understanding of these cases and a rational interpretation of the clinical course and end-results of the ligation of this artery presuppose a detailed knowledge of its surgical anatomy (Fig. 2).

*Anatomy*—In studying the subject, it soon becomes apparent that the common carotid artery and its branches present frequent abnormalities. The artery often varies considerably as to its site of origin, length, size, number of branches and level of bifurcation, not only in different subjects, but on opposite sides of the same neck. One of the most frequently performed operations on the Head and Neck Service at the Memorial Hospital is the ligation of the external carotid artery and its branches. The staff have noted for years that the carotid artery bifurcation may be as high as the hyoid bone or as low as the cricoid cartilage, and only about half occur at the level of the upper border of the thyroid cartilage, which is said to be the normal location.

## LIGATURE OF COMMON CAROTID ARTERY

The internal carotid artery occasionally is absent. The ascending pharyngeal artery is derived from the internal carotid in 5 per cent of the cases and separately from the internal and external arteries in about 2.5 per cent of the cases. Wyeth reports extra or abnormal branches of the external carotid artery in 39 per cent, and points out the fact that in the majority of cases there is no attempt at symmetrical arrangement of the vessels on the two sides.

Relative to the anatomy of the vessels at the base of the brain, Windle,<sup>42</sup> studying the anatomy of the circle of Willis, performed 200 autopsies, and from the study of this material found that in 124 cases (62 per cent) the con-

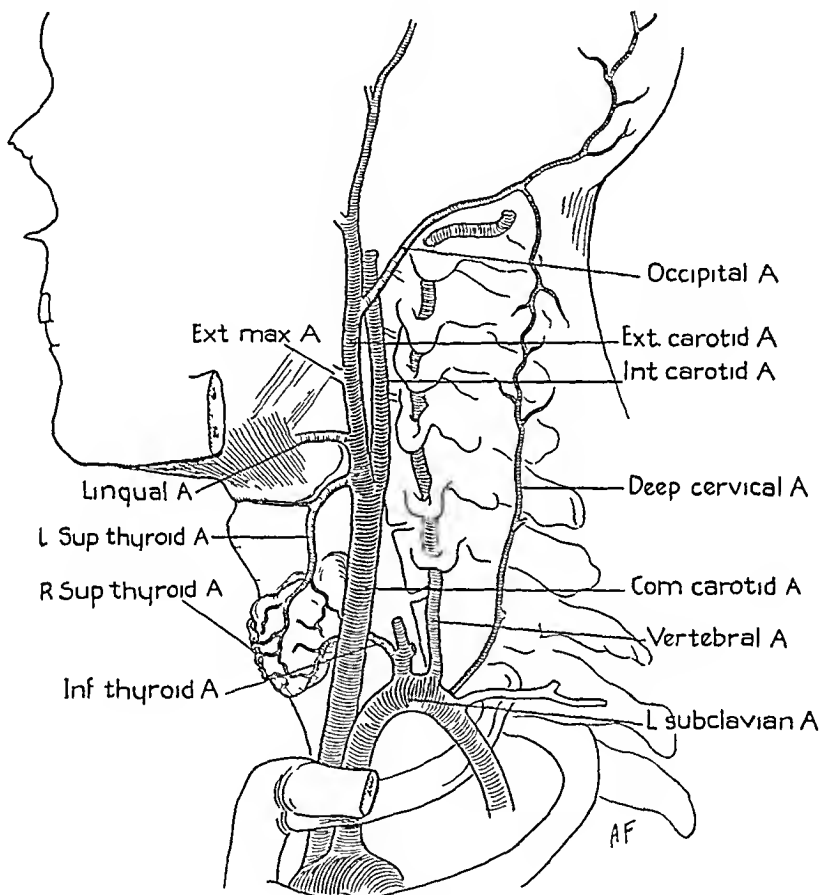


FIG 2 —Showing the extracranial collateral circulation

ditions which obtained were not those which are described in the text-books as being the normal arrangement. Such marked and frequent abnormalities occurring in the main arteries of the neck and base of the brain suggest that an anatomic factor may play a prominent rôle in the postoperative events following the ligation of the common carotid artery.

It is commonly supposed that following the ligation collateral circulation can be established by the free communication which exists between the carotid arteries of opposite sides, both without and within the cranium, and by enlargement of the subclavian artery on the involved side. The chief communications outside the skull take place between the superior and inferior thyroid arteries and the deep cervical artery with the descending branch of

the occipital Communication in the midline of the face takes place between the superior and inferior labial arteries, the angular arteries, and the frontal branches of the superficial temporal arteries The vertebral artery takes the place of the internal carotid artery within the cranium

Although most authorities agree that eventually circulation is reestablished to the cerebral hemisphere of the ligated side by the above devious route, we lack conclusive proof that such a phenomenon occurs or could occur quickly enough to prevent permanent cerebral damage even after gradual clamp occlusion of one common carotid artery It should also be pointed out that if reestablishment of adequate cerebral circulation were dependent upon the development of a collateral circulation downward through the carotid bulb, then ligation of the internal carotid artery would be a fatal procedure and it is well known that such is not the case One might also ask where the collateral circulation comes from in instances of the ligation of both common carotid arteries, which has a reported operative mortality of only 9 per cent (Wyeth)

Wortis<sup>44</sup> reports a case in which the patient developed a complete cerebral hemiatrophy during an eight-year period following ligation of one common carotid artery for cavernous sinus aneurysm Here the collateral circulation was obviously inadequate from the beginning and did not improve with time Many immediate ligations have been performed upon good subjects, and the mortality rate has been low In such cases the collateral circulation could not have been established so promptly as to prevent an immediate cerebral anemia, so it appears that the circulation to the brain in these favorable cases was adequate without the common carotid The cerebral changes and resulting symptoms may largely depend on the size and number of large vessels originally supplying blood to the brain rather than upon the ability of the external carotid artery to obtain blood from its fellow of the opposite side and, by reversing its flow, to send it by way of the internal carotid to the brain It appears as though collateral circulation in relation to common carotid artery ligation is not as important as was formerly believed

Evidently stimulated by reported operative mortalities ranging as high as 54.5 per cent (LeFort) and 41 per cent (series of 789 cases reported by Wyeth), surgeons modified the operative technic and invented devices for the gradual occlusion of the artery in an attempt to make the operation safer by seeking to establish an adequate collateral circulation Crile,<sup>5</sup> in 1901, reported a spring-end screw clamp, the lower blade was slightly longer than the upper and curved upward at its free end so as to encircle and grasp the artery firmly By means of the thumb-screw the rubber covered blades could be slowly closed over a period of hours (Figs 3 and 4) Halsted<sup>22</sup> advised small aluminum bands for the gradual occlusion of the artery while Matas<sup>29</sup> recommended strips of fascia lata Neff,<sup>32</sup> in 1911, reported an ingenious hinged device of two aluminum blades which are placed around the artery and held apart by numerous turns of catgut which, when gradually absorbed by nature, allows the blades to be brought together by rubber bands, thus

## LIGATURE OF COMMON CAROTID ARTERY

producing a gradual automatic occlusion of the common carotid artery at one operation. Where time permits, it has been the practice, on the Head and Neck Service, to use the Crile clamp in ligating the common carotid artery.

*Operative Procedure*—A 1 per cent novocain solution, containing ten

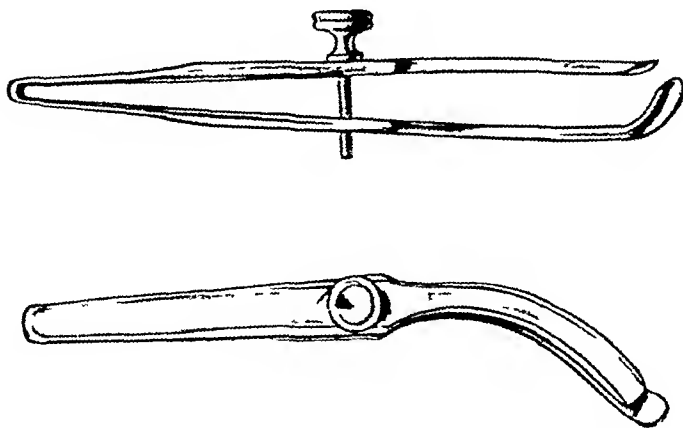


FIG 3—Clamp devised by Crile for gradual occlusion of the common carotid artery

drops of adrenalin to the first ounce, is injected in the skin for a distance of 4 cm along the anterior border of the lower third of the sternomastoid muscle. The platysma is incised, the sternomastoid muscle retracted laterally,

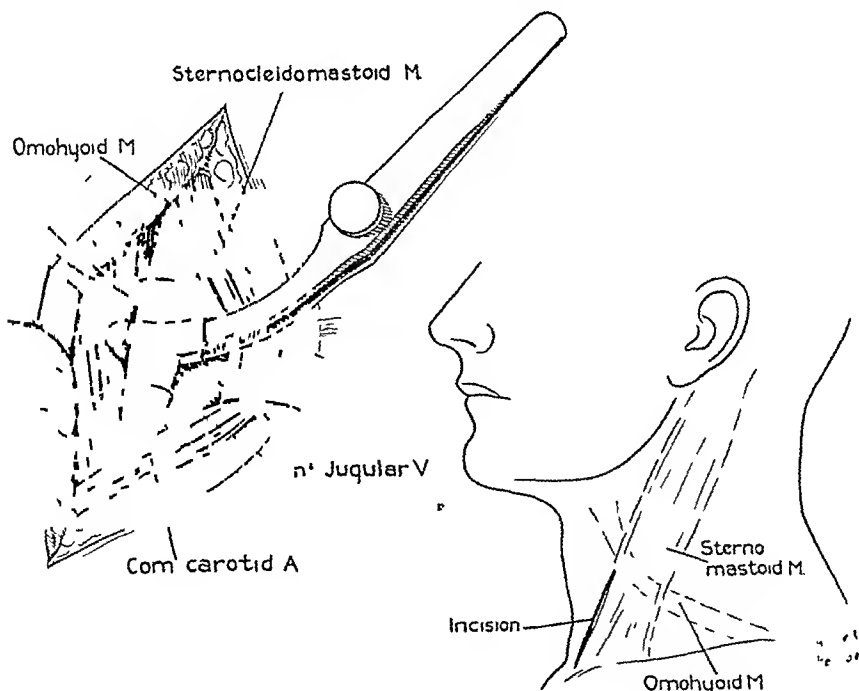


FIG 4—Illustrating ligation of the common carotid artery using the Crile clamp

and the common carotid artery located just below the crossing of the omohyoid muscle. The carotid sheath is incised and separated from the artery for a distance of 1 cm, then the Crile clamp is placed about the artery and two, untied, No 2 chromic catgut sutures placed around the artery, one above



and one below the clamp. The wound is packed open and the clamp slowly screwed shut over a period of 24 hours. At the end of this time the packing is removed, ligatures tied and the clamp removed. If cerebral symptoms develop during the gradual closing of the clamp, its jaws can be reopened and the flow of the blood reestablished. One case in this series developed cerebral signs at the end of six hours. The clamp was unscrewed, but the patient became cyanotic and died. To be avoided in this procedure are such accidents as pressure necrosis of the artery walls, wound infection, hemorrhage and vagus and sympathetic nerve damage.

### CASE REPORTS

**Case 1**—G T, male, age 46, was admitted to Memorial Hospital November 10, 1925, complaining of soreness on the inside of his left cheek. He had been a heavy pipe smoker and also chewed tobacco.

*Examination* revealed a granular, ulcerated and indurated lesion 6x8 cm involving the left buccal mucosa. Teeth were in poor condition and directly in contact with much of the growth. One node was palpable in the carotid bulb region. Biopsy revealed squamous cell carcinoma, Grade 1, radioresistant.

*Indication for Ligation*—Treatment was first by extraction of teeth, following which high voltage roentgenotherapy and interstitial radium were employed. The disease in the cheek was not well controlled and the neck node increased in size. His general condition became worse because of infection and sepsis, and on March 3, 1926, an operation was undertaken with the idea of ligating the left external carotid artery. This vessel was found to be surrounded by tumor tissue and the common carotid artery was therefore isolated and with great difficulty ligated. The patient's temperature rose immediately to 105.8° F, respirations to 160, and death occurred 36 hours later.

**Case 2**—J E N, male, age 59, was admitted to Memorial Hospital June 7, 1926, because of a lump in the left submaxillary region of six months' duration. A painful ulcer had appeared on the tip of the tongue five weeks before admission.

*Examination* revealed a firm, ulcerated growth 2½x1½ cm on the left anterior floor of mouth extending from the frenum of the tongue backward to the base of the tongue. A large metastatic node was present in the left submaxillary region. Biopsy showed squamous cell carcinoma.

*Indication for Ligation*—Treatment consisted of high voltage roentgenotherapy combined with radium element pack radiation to both sides of the neck, supplemented by interstitial radium in the form of gold filtered radon seeds in the primary lesion. A left radical neck dissection was performed November 25, 1927, and the wound apparently healed well, but two months later it broke down and severe hemorrhage occurred from the upper part of the neck wound where an area of slough had occurred. The common carotid artery was exposed by this process and had to be doubly ligated with chromic catgut and severed.

*Result*—There was apparently no immediate ill effect following ligation of the common carotid artery. However, patient's general condition slowly became worse and on February 12, 1928, 18 days after operation, he had a sudden attack of dyspnea without developing any neurologic signs. He recovered from this and went on until April 7, 1928, when he suddenly went into coma, developed generalized convulsions and died. Autopsy showed diffuse cellular epidermoid carcinoma, Grade 3, in the neck, chronic suppurative arteritis of the common carotid artery and purulent pneumonia. No cerebral examination was permitted.

**Case 3**—J C, male, age 53, was admitted to Memorial Hospital March 26, 1927, complaining that his gums did not heal following the extraction of four teeth three and one-half months previously, and that he had developed difficulty in opening his mouth and

swallowing solid food Three weeks before admission a lump had appeared in the left neck

*Examination* revealed a partially ulcerated and indurated granular lesion 3 cm in diameter on the posterior part of the left upper alveolar ridge A node  $2\frac{1}{2}$  cm in diameter was noted anterior to the left carotid bulb Biopsy of the primary lesion showed epidermoid carcinoma, Grade 3

*Indication for Ligation*—Treatment consisted of alcohol injections of the second and third divisions of the left fifth cranial nerve, extraction of upper left molar tooth, radium element pack to left upper neck, and gold filtered radon seeds both into the primary lesion and the neck node Necrosis and sequestration of the ascending ramus of the mandible occurred On April 2, 1928, a left radical neck dissection was performed The wound healed well and there was no evidence of disease until September, 1928, when new growth was noted in the left base of tongue Gold filtered radon seeds were inserted and regression was complete Two months later an indefinite mass was noted in the tissues of the left neck This was exposed and found to be a necrotic metastatic mass containing foul-smelling, thin, grayish, purulent material The cavity extended upward to the left tonsillar region Both internal and external carotid arteries were involved in this necrotic process, and both were quite friable

*Operative Procedure*—The common carotid artery was exposed and two No 2 chromic catgut ligatures were placed around it with a Crile clamp between them During the course of 24 hours the clamp was slowly tightened and the ligatures then tied

*Result*—No ill effects were noted for two days except for nocturnal disorientation On the third day right-sided hemiplegia occurred followed by coma and death 48 hours later, five days after the ligation of the common carotid artery

**Case 4**—W J F, male, age 34, was admitted to Memorial Hospital December 30, 1927, complaining of pain in the left cheek of eight weeks' duration

*Examination* showed widespread intra-oral leukoplakia, and, in the left buccal mucosa at the level of the third molar tooth, a deep ulcer  $2\frac{1}{2}$  cm with rolled, indurated edges A group of enlarged nodes was palpable in the left upper neck Wassermann was negative Biopsy showed epidermoid carcinoma, Grade 2, radioresistant

*Indication for Ligation*—Treatment consisted of a combination of high voltage roentgenotherapy and radium element pack to both sides of neck and cheek followed by the insertion of gold radon seeds directly into the growth In February, 1928, there was marked temporary improvement with apparent regression of the primary lesion and marked regression of the neck nodes Osteomyelitis of the left mandible and recurrence of disease in the left submaxillary triangle occurred, and a limited upper neck dissection was carried out The tissue removed revealed recurrent carcinoma Sloughing of the wound followed and on September 29, 1928, hemorrhage occurred from the left neck and mouth This was controlled by packing, but during the evening a severe hemorrhage of about 800 cc occurred and patient went into shock Hemorrhage was controlled by pressure and his general condition supported by hypodermoclysis The left common carotid artery was exposed just above the level of the sternoclavicular articulation and ligated The patient was given a transfusion of 700 cc of whole blood On the following day, evidence of hemiplegia appeared and patient died three days later after his temperature had risen to  $105.2^{\circ}$  F, pulse 168, respirations 58

**Case 5**—D G S, male, age 54, was admitted to Memorial Hospital March 4, 1927 Six months previously patient noted a mass in the left neck Repeated examinations revealed no primary tumor, and a complete radical left neck dissection was performed five months after onset of symptoms Later, a biopsy was removed from a suspicious lesion in the left tonsil and this proved to be carcinoma

*Examination*—On admission the neck wound was entirely healed The throat appeared innocent and no infiltration was noted in the region of the tonsil from which the biopsy had been removed

*Pathologic Diagnosis*—Papillary epidermoid carcinoma, Grade 2, radioresistant, neck and tonsil

*Indication for Ligation*—Treatment consisted of a combination of external radiation with the radium element pack to left neck followed by implantation of gold filtered radon seeds into the left tonsil. Eight months later a node appeared in the left neck and this was treated by the implantation of gold radon seeds. Disease in the neck was never entirely controlled and in August, 1928, ulceration occurred exposing the common carotid artery. This was surrounded by recurrent disease. The cancerous ulcer was excised and the common carotid and internal carotid arteries were removed.

*Result*—Patient made an uneventful recovery from the above procedure, but disease again recurred in the neck and he died of cancer and hemorrhage, March 27, 1930, three years after admission to the hospital and one year and seven months after excision of the common carotid artery.

**Case 6**—J. B., male, age 63, was admitted to Memorial Hospital March 31, 1928, with a history of pain in the region of the left lower molar teeth of two months' duration. Following the extraction of teeth in this region, the gums failed to heal and, at another hospital, the involved area was cauterized with a solution of copper sulphate.

*Examination* revealed a bulky tumor involving the posterior half of the lower alveolar region and extending into the floor of the mouth. The lesion was sloughing and infected. The biopsy was reported as showing papillary epidermoid carcinoma, Grade 1.

*Indication for Ligation*—Treatment was by a combination of high voltage roentgenotherapy to both sides of the neck together with interstitial radon in the primary growth. At first regression appeared complete, but later an extensive slough developed and roentgenograms revealed an extensive infiltration into the left inferior maxilla. Necrosis and infection were so extensive as to require common carotid artery ligation which was performed June 12, 1928.

*Result*—Patient died the following morning.

**Case 7**—C. H., male, age 42, was admitted to Memorial Hospital September 26, 1929, complaining of soreness of the left cheek of six months' duration.

*Examination* revealed a neoplasm occupying the posterior portion of the left cheek, infiltrating the masseter muscle and extending medially to invade the soft palate and anterior tonsillar pillar. A firm mass was palpated below the mandible and attached to the jaw. Biopsy was reported as squamous carcinoma, Grade 1.

*Indication for Ligation*—Treatment consisted of radium element pack applications to both sides of neck, and implantation of gold radon seeds into the neck mass. On October 10, 1929, the left mandible and adherent neoplastic tissue were excised. A large open defect resulted and was allowed to heal. During the next 15 months several attempts at plastic closure were carried out with only partial success. In March, 1931, a metastatic node 3.5 cm in diameter was found in the left posterior cervical triangle. On March 16 this mass was excised, but it was found to be closely adherent to the common carotid artery at the level of the bifurcation. The artery itself seemed greatly thickened and constricted, and no pulsation was palpable. On the other hand, the external carotid artery was patent and pulsating normally.

*Operative Procedure*—March 30, 1931. The common carotid artery was doubly ligated and divided at a point 1 cm above the sternoclavicular junction. A modified radical neck dissection was then carried out. The vagus nerve was divided and the internal jugular vein excised. The internal and external carotid arteries were ligated and divided above the tumor.

*Result*—Following ligation, patient developed bradypnea which was relieved by atropin. Three days postoperative, there was a transient diminution of vision for about 15 minutes and slight deviation of tongue to the left. Skin metastases were noted on April 20, 1931, and removed. Healing occurred and there was no evidence of disease until September, 1931, when radiation necrosis developed and on September 20, 1931,

patient had a sudden severe hemorrhage, apparently from the stump of the common carotid artery, and died

**Case 8**—H L, male, age 40, was admitted to Memorial Hospital August 5, 1930 complaining of a sore tongue and loss of weight of six months' duration

*Examination* revealed a bulky growth involving the entire base of tongue and infiltrating the right tonsillar pillar and floor of mouth. Biopsy showed the lesion to be a squamous carcinoma, Grade 2

*Indication for Ligation*—Treatment consisted of radiation by means of the radium element pack to both sides of the neck supplemented by insertion of gold seeds. Radiation necrosis and infection occurred in the tongue, which was removed by cautery excision November 17, 1930. As hemorrhage was imminent it was decided to ligate the external carotid artery on the right side. On exposing this area, however, metastatic nodes were encountered and the tissues were friable, due to radiation effect

*Operative Procedure*—A ligature applied around the lingual artery cut through it. The external carotid artery was lacerated, and, therefore, a Crile clamp was applied to the common carotid artery which was slowly occluded during a 30 minute interval. The vessel was then ligated

*Result*—Following ligation, patient developed slight incoherence of speech which might have been due to local tongue condition. However, mental aberrations occurred, patient became uncooperative and unruly and required physical restraint. On the third postoperative day, incontinence developed, followed by weakness of the left arm and leg which rapidly progressed to complete left-sided paralysis. Pulse became rapid and irregular, temperature rose to 105.8° F, and patient died

*Autopsy*—Postmortem examination revealed edema of the larynx, edema of the brain, lobar pneumonia, acute pleuritis, septic spleen and polyserositis

**Case 9**—C Z, male, age 45, was admitted to Memorial Hospital August 28, 1930, complaining of discomfort in the left upper jaw and a small painless growth in the alveolar ridge of two months' duration

*Examination* revealed an ulcerated, fissured, papillary growth in the posterior portion of the left hard palate and extending downward into the soft palate. In the posterior half of the left submaxillary triangle, one node was palpable and an indefinite mass was noted over the left carotid bulb. Biopsy of the primary lesion showed it to be squamous carcinoma, Grade 2

*Indication for Ligation*—Treatment consisted in radiation by means of the radium element pack to both sides of neck, supplemented by implantation of gold seeds into the primary lesion. The original growth disappeared, but in October, 1930, gold filtered radon seeds were implanted in the neck nodes, and two months later ulceration was noted in the mouth at the angle of the jaw. This ulcerated area enlarged, became necrotic and extended into the left anterior tonsillar pillar. Osteomyelitis of the superior maxilla occurred, resulting in trismus and marked swelling of the soft parts. Hemorrhage from the tonsillar area occurred April 27, 1931. On May 4, 1931, a radical neck dissection together with partial resection of the mandible was carried out and a 500 cc whole blood transfusion was given. Nine days postoperative a severe hemorrhage occurred from the wound and two days later the common carotid artery was exposed just above the clavicle

*Operative Procedure*—A Crile clamp was applied, slowly closed, and then ligated. A 500 cc whole blood transfusion was given. There was no sign of hemiplegia postoperatively. Temperature rose to 102.6° F, pulse 130, and respirations 80, and patient died five days after the operation

*Autopsy*—Postmortem examination showed carcinoma of the left superior maxilla, radiation slough left side of neck, bronchopneumonia, edema of the lung, septic splenitis, and edema of the meninges

**Case 10**—H B K, male, age 56, was admitted to Memorial Hospital August 11,

1931, giving a history of an ulcer in the right side of tongue of 15 months' duration. A cautery excision had been performed in October, 1930, and bilateral neck dissections were performed, but examination of the neck tissues was negative for carcinoma. In December, 1930, the tongue presented evidence of recurrence and was again excised. In March, 1931, a mass appeared in the upper part of the right neck. This continued to enlarge during roentgenotherapy and implantation of gold seeds.

*Examination* revealed scarring of the tongue, due to previous operations, but no evidence of disease. In the right side of neck there was a hard fixed mass 12 cm in diameter. It was obviously surrounding and invading the great vessels of the neck, and extended almost to the clavicle.

*Indication for Ligation*—The case was regarded as probably hopeless, but a radical excision was decided upon and attempted August 17, 1931. The common carotid artery was ligated and the phrenic nerve divided. At this stage the patient went into shock and died immediately.

*Pathology*—Examination of excised specimen revealed metastatic squamous carcinoma, Grade 2.

*Result*—Patient died immediately after ligation. The excised artery showed moderate sclerosis but no thrombi.

**Case 11**—B Z, male, age 50, was admitted to the Memorial Hospital December 5, 1932, with a history of attacks of asthma and tonsillitis and periods of alcoholic excess, and complaining of a painless swelling in the right side of the neck of three months' duration which had slowly been increasing in size. Five weeks before admission a tonsillectomy had been performed, following which slight discomfort in his throat and a sensation of choking on eating solid food were noted.

*Examination* revealed scars in both tonsillar regions, and in the right tonsil fossa there was a deeply infiltrating submucous mass 4 cm in diameter. In the right side of the neck, anterior to the carotid bulb, a firm movable node 2½ cm in diameter was noted and proven on aspiration biopsy to be metastatic carcinoma.

*Pathology*—Report of the operative specimen revealed carcinoma structure, too altered by radiation to permit diagnosis of the type.

*Indication for Ligation*—Treatment was first by radium element pack exposures to each side of the neck followed by the implantation of gold radon seeds into the neck node. The primary tonsillar tumor regressed completely but the neck mass persisted. Secondary implantation of gold radon seeds was again unsuccessful in eliminating the cervical disease and, on June 7, 1933, a right radical neck dissection was performed. A mass 5 cm in diameter was found overlying and encircling the carotid bulb.

*Operative Procedure*—The common carotid artery was compressed by digital pressure for a period of five minutes. As no untoward symptoms occurred, the artery was doubly ligated and severed and removed with the metastatic mass. The internal and external carotid arteries were also ligated and severed at a point just below the level of the mastoid process. The vagus and phrenic nerves were dissected and preserved.

*Result*—Convalescence was uncomplicated except for the occurrence of a slight, well localized area of osteomyelitis of the mandible. Patient is now well and free of disease four years and four months from the date of ligation.

**Case 12**—C S, female, age 69, was admitted to Memorial Hospital February 26, 1932, complaining of swelling in the left neck of one year's duration and a sore throat of six months' duration.

*Examination* revealed a fixed, ulcerated, granular lesion 2.5 cm in its longest diameter involving the left tonsillar fossa. A fixed metastatic mass 5 cm in diameter was located in the left upper neck just below the tip of the mastoid process. Biopsy of the primary lesion was reported as papillary epidermoid carcinoma, Grade 2, radiosensitive.

*Indication for Ligation*—Treatment was carried out by divided doses of roentgenotherapy to both sides of the neck given by means of a 700 K-V machine. This was followed by the implantation of gold filtered radon seeds in the neck mass. After the

usual radiation reaction, the primary tumor regressed completely, but the original mass showed only partial regression and new metastatic deposits appeared lower in the neck. The residual disease in the neck was again treated with gold filtered radon seeds and the new nodes were treated in a similar fashion. Suppuration of the middle ear occurred and roentgenograms revealed an area of destruction in the squamous portion of the left temporal bone. On December 30, 1935, a partial neck dissection was performed and a hard irregular mass 3.4x2 cm was dissected away from the carotid artery. Pathologic examination of the material removed showed old hyaline fibrosis with few degenerated calcified nonviable tumor cells. The wound broke down and a large necrotic area was exposed. When this became cleaner a large necrotic area was revealed and the underlying common carotid artery exposed. Because of the danger of hemorrhage, the common carotid artery was ligated March 7, 1936.

*Operative Procedure*—Under local anesthesia, the artery was exposed in a clean area 3.5 cm below the ulcer. Two heavy chromic ligatures were placed around it and a Crile clamp between them. The clamp was closed to within six revolutions of complete closure and from there on the clamp was closed a quarter of a turn every hour. Five hours later a severe hemorrhage occurred and the clamp was screwed down tightly, the ligatures tied, and the hemorrhage controlled. Slight deviation of the tongue occurred to the left, but no signs of hemiplegia were noted. A six hundred cubic centimeter whole blood transfusion was given followed by an infusion and clysis. The following day hemorrhage from the wound recurred, but this was found to have its origin from the external and internal carotid arteries at about the level of the carotid bulb. After ligating these arteries the bleeding was controlled, but the patient went immediately into shock. Blood pressure dropped to 90/70, unconsciousness occurred, and paralysis of the right arm was noted. Death occurred without the patient's regaining consciousness, 24 hours later.

*Result*—Patient died 24 hours after combined ligation of the common carotid, external and internal carotid arteries on the left side. Autopsy revealed, in addition to the operative findings, softening and ischemia of the entire left cerebral hemisphere, most marked in the parietal area, the precentral and postcentral gyri.

**Case 13**—G. F. A., male, age 53, was admitted to Memorial Hospital March 28, 1933, complaining of epistaxis, swelling of the right upper neck, hoarseness and pain in the right side of the head of one year's duration. Roentgenotherapy had been administered elsewhere.

*Examination*—Local examination revealed edema of the extrinsic larynx without definite evidence of a primary tumor in this region. There was a firm metastatic node in the region of the right carotid bulb measuring 5 cm in diameter. Aspiration biopsy revealed this to be squamous cell carcinoma.

*Indication for Ligation*—Treatment consisted of implantation of gold filtered radon seeds in the neck mass followed by negligible regression of disease. A right radical neck dissection was performed July 17, 1933, and it was found possible to separate the mass from the common carotid artery. Gold filtered radon seeds were implanted in the tumor bed. Four weeks after this operation, the wound broke down exposing the common carotid artery for a distance of 10 cm and, on September 2, 1933, in view of the danger of severe hemorrhage, the right common carotid artery was ligated.

*Operative Procedure*—A Crile clamp was placed on the common carotid artery and two loosely tied No. 2 chromic ligatures were placed, one above and one below. Gradually, over a period of 36 hours, the jaws of the clamp were compressed. Then the ligatures were tied.

*Result*—Immediately after the sutures were tied, the patient went into coma, developed a well marked left hemiplegia, and death occurred 48 hours later. Autopsy revealed metastatic carcinoma of right cervical nodes, radiation ulcer, thrombosis of the common carotid artery, terminal lobar and lobular pneumonia and generalized arteriosclerosis.

**Case 14**—L S, female, age 60, who had been treated for coronary disease for several years, was admitted to Memorial Hospital September 26, 1933, complaining of an enlarging, painful mass in the neck of four months' duration

*Examination* revealed a firm, slightly nodular, moderately movable, indurated mass in the left lobe of thyroid, displacing the trachea slightly to the right. Aspiration biopsy showed the mass to be cancer

*Indication for Ligation*—At operation, October 23, 1933, the tumor mass, 6 cm in diameter, was found involving the left lobe and isthmus of thyroid. At one point the tumor was found to infiltrate the walls of the common carotid artery. The artery was compressed for a period of five minutes, and as there were no untoward symptoms the vessel was ligated and excised together with the neoplasm. The vagus nerve was dissected with some difficulty, and at this point the patient went into collapse from which she gradually recovered. The internal and external carotid arteries were also sectioned above the thyroid

*Pathology*—Histologic report was diffuse, anaplastic, solid, spindle and polyhedral cell carcinoma of thyroid, Grade 3

*Result*—Postoperative course was uneventful. No neurologic changes occurred. One year later, October, 1934, she developed paralysis of the left vocal cord and weakness of the left lower extremities with exaggerated tendon reflexes on the left side. There was no clinical evidence of recurrence of disease. She was last seen in the Clinic April, 1935, at which time there was no change

**Case 15**—L Y, male, age 60, was admitted to Memorial Hospital May 18, 1936, with a history of a painful ulceration in the mucosa of the right cheek of two months' duration

*Examination* revealed an ulcerated, indurated, infiltrating new growth occupying the major portion of the right buccal mucosa, surrounded by a zone of leukoplakia which was prominent also on the left buccal mucosa. Moderate trismus, dental sepsis and puffiness in the right preauricular region were noted. There was a metastatic node 2.5 cm over the right carotid bulb. Histologic examination showed the primary lesion to be squamous carcinoma, Grade 2

*Indication for Ligation*—Treatment consisted of roentgenotherapy and interstitial radon to the cheek lesion and neck node. This was followed by temporary regression of disease and local cheek recurrence in two months. This was treated by radical resection of the mandible and involved soft tissues. A preliminary ligation of the right external carotid and lingual arteries was performed. Further sloughing of soft tissues occurred and the common carotid artery was exposed in the base of the open wound. Recurrence was again noted, this time surrounding the artery. Ligation of the common carotid artery was performed because of danger of perforation and hemorrhage

*Operative Procedure*—A Crile clamp was applied, January 15, 1937, and the artery compressed slowly. During the next six hours the jaws of the clamp were slowly compressed. At the end of this time patient suddenly developed stertorous breathing of the Cheyne Stokes type. He became spastic, cyanotic, and died suddenly

**Case 16**—H J S, male, age 50, was admitted to Memorial Hospital December 9, 1936. One and one-half years previously a sore had developed at the right corner of mouth. This was treated with radium and healed. Later on he developed nodes in the right neck. These were excised and then treated with roentgen and radium therapy, but sloughing of the wound occurred with exposure of the mandible, mouth and deep neck structures

*Examination* revealed extensive destruction of the lower half of the face and submaxillary triangle of the neck on the right side. The mandible, obviously necrosed, was exposed and showed the roots of the few remaining teeth. The whole area was covered with pale pink, coarsely granular, recurrent cancer. Biopsy was reported as squamous carcinoma

*Indication for Ligation*—Preliminary procedure, because of the potential danger of

severe hemorrhage, prior to excision of the whole involved area with subsequent plastic repair

*Operative Procedure*—December 12, 1936 The right common carotid artery was exposed, under local anesthesia, in the lower part of the neck away from the wound. A Crile clamp was placed on the vessel. During the course of 48 hours the clamp was slowly closed. At the end of that time the vessel was completely occluded and ligated with chromic catgut. No untoward symptoms developed at any time except slight frontal headache.

*Postoperative Course*—The carotid wound, which was packed open and not sutured, healed completely. The patient developed pneumonia and an encapsulated pleural effusion from which he recovered with supportive therapy. General condition improved markedly and, on January 6, 1937, cautery excision of the entire lesion was performed. Patient stood the operation well and was improving slowly until March 2, 1937, when sudden unconsciousness developed accompanied by cyanosis and severe dyspnea, and death occurred about 12 minutes later. It was problematic whether death was due to laryngeal edema or cerebral embolus.

*Result*—Patient died two months and 20 days after ligation of the common carotid artery. Cause of death unknown.

**Case 17**—J. R., female, age 56, was admitted to Memorial Hospital January 16, 1935, complaining of an ulcer below the left ear of three years' duration. She had received a course of radiation for tuberculous nodes 20 years previously. She had had typical telangiectasia, discoloration and mottling ever since her treatment but had never had ulceration until three years before admission. She had received no treatment for the ulceration.

*Examination* revealed a typical radiation burn measuring about 15 cm just behind the angle of the left jaw. In the center there was an irregularly round ulceration measuring 5 cm in diameter. The borders were firm, partially raised, and there was infiltration to a depth of 6 mm. Biopsy was reported as squamous carcinoma, Grade 2.

*Indication for Ligation*—Twenty-nine gold seeds for a total of 49.9 mc were inserted into the lesion. Following treatment there was apparently complete regression of disease. Another indurated ulcer developed four months later. Specimen was reported as showing squamous carcinoma, and she was admitted to the hospital for excision of the ulcer and plastic repair. The internal carotid artery was invaded by disease and this was accidentally lacerated during operation. For this reason the common carotid artery ligation was carried out to control hemorrhage.

*Operative Procedure*—The common carotid artery was compressed by digital pressure for a few minutes and as no evidence of cerebral anemia occurred, the artery was ligated. The common carotid artery and carotid bulb were removed. During the dissection of the artery from the vagus nerve, surgical shock occurred.

*Result*—Immediately after the operation patient developed partial temporary paralysis of the right arm and leg. She recovered from the shock and paralysis after 24 hours. Patient is alive, with new metastatic disease in the left supraclavicular space, eight months after ligation.

**Case 18**—W. M., male, age 47, was admitted to Memorial Hospital June 16, 1937, because of a small lump in the left neck of ten years' duration. It was not painful and remained about 4 cm for seven years, after which time it began to increase steadily in size.

*Examination* revealed an ovoid, smooth, moderately firm mass 8 cm in its longest diameter in the left neck, centered over the carotid bifurcation. It extended downward and deeply into the sternomastoid muscle and apparently under the carotid artery (Fig 5). Its consistency suggested a cyst rather than a tumor. Partial paralysis of the left side of the larynx was noted.

*Indication for Ligation*—Treatment consisted of external radiation. The mass did



not regress and surgical excision was decided upon. At the time of operation the mass was found to encircle the common carotid artery.

*Operative Procedure*—Under local infiltration anesthesia, a modified Bastianelli



FIG 5—Case 18 Carotid body tumor

incision was carried out and the sternomastoid muscle, together with the internal jugular vein and common carotid artery, was removed with the mass. Before cutting across the common carotid artery a Crile clamp was placed around it and clamped for a period of

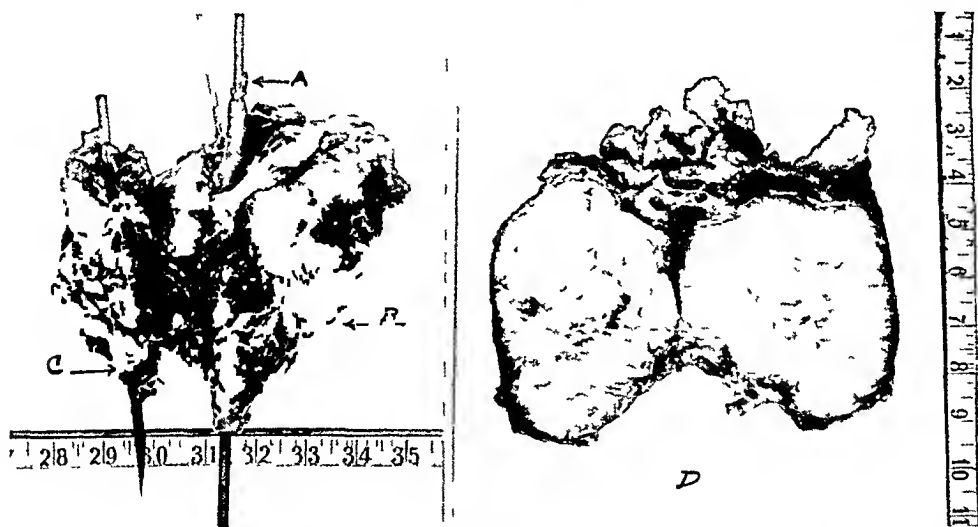


FIG 6—Case 18 (Carotid body tumor). Gross specimen (A) Common carotid artery (B) Tumor (C) Internal jugular vein (D) Cut section of tumor

20 minutes. No hemiplegia or untoward symptoms resulted. The artery was then ligated just above the clavicle. The internal carotid and external carotid and its branches were also ligated. The vagus nerve was saved by dissecting it from the mass.

*Result*—The immediate postoperative course was uneventful. The wound healed by first intention. A definite Horner's syndrome appeared after operation, together with a paralysis of the left glossopharyngeal, hypoglossal, and recurrent laryngeal nerves. Complete eye examination revealed no retinal changes. Left pupil was smaller than the right and did not react to light. There was slight ptosis of the upper lid. There was no diminution of sweating on the left side of face. The postoperative edema of the left side of the larynx was of transient nature.

*Pathology*—*Gross*. An encapsulated, multilobular tumor measuring 7.5x4 cm. The carotid artery grooved the mass on its superficial aspect but was separable on blunt dissection. Both a section of the carotid artery and a similar length of jugular vein were

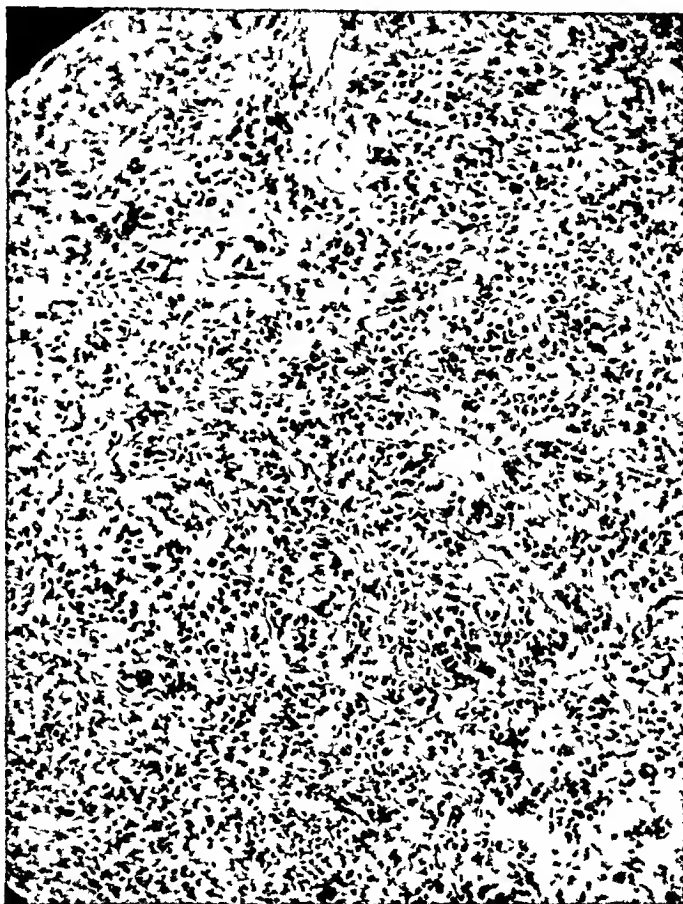


FIG 7—Case 18 (Carotid body tumor). Photomicrograph showing the distinctive polyhedral granular cells arranged in compact groups without lumen.

removed with the tumor (Fig 6). On section the mass was soft, grayish to pinkish-gray. Though consistent anatomically with carotid body tumor, it appeared too soft and cellular on section. The surrounding soft tissue contained a few slightly enlarged nodes. *Microscopic Diagnosis*. Carotid body tumor (Fig 7).

*Result*—Following operation temperature did not rise above 100.8° F, and went down to normal in three days. Pulse rate rose to 108, and gradually subsided, but was running about 88 at time of discharge, 13 days after the operation. The patient is alive and well, 51 months after operation.

**Case 19**—M. R., male, age 27, was admitted to Memorial Hospital Clinic November 2, 1937, with a chief complaint of repeated rather large hemorrhages from the right upper alveolar ridge and mucosa of cheek. The patient had a fairly large birthmark on the right side of his face which did not change a great deal until he was age 17, when the

involved side of the face was injured while playing basket-ball by violently striking another player's head. Following this, rapid tumor growth took place during the next three years and at age 20, an operation for removal was attempted but not completed due to profuse bleeding, and at that time the right external carotid artery was ligated. Later, skin grafts were applied to the right side of the face, for the following two years, many injections of sclerosing solutions were attempted without success. At age 25, a right upper tooth was extracted and profuse bleeding resulted, and aspiration of some of the blood caused a pulmonary abscess. A week before admission to Memorial Hospital Clinic he developed sharp pain in the left side followed by cough and expectoration and fever of four or five days' duration. Coincident with this, bleeding occurred from the mucosa of the right cheek and upper alveolus and several sharp hemorrhages resulted in the loss of several quarts of blood.

*Examination*—The tissues of the right side of the face, including the lower eyelid, the zygomatic region and the submaxillary area, showed a large, purplish, soft, compressible, rather hot, pulsating, cavernous type of hemangioma. A portion of the skin of the cheek showed a good deal of scarring and well healed Thiersch grafts. The entire lesion was about 16 cm in its longest dimension and in some areas at least 6 cm in thickness. In the temple region there was an area of port wine-stain involvement of the skin. In the upper right neck there was an old, well healed, oblique operative scar of the previous external carotid artery ligation. A loud bruit was heard over the infra-orbital and temporal portion of the lesion. The right external jugular vein was enlarged to a diameter of about 2 cm. The right upper alveolar ridge was granular, soft and the underlying bone crepitated, and on manipulation bleeding from this area occurred. If patient leaned forward or lowered his head, sharp bleeding occurred.

Eye consultation showed a right exophthalmos of  $3\frac{1}{2}$  Mm, a pale right optic nerve, and an enlarged right retinal vein. Vision of the right eye was limited to distinguishing fingers at three feet. Ophthalmic diagnosis: Hemangioma of the right orbit and right optic atrophy.

Chest examination revealed the physical findings of fluid in the left chest, and a roentgenogram showed evidence of the presence of an infiltration in the left base and a left pleurisy with effusion.

Severe secondary anemia was evidenced by the preoperative blood examination which showed a hemoglobin of 20 per cent, RBC 1,696,000, WBC 5,200, and considerable variation in size and shape of the red blood cells. Temperature normal, pulse 92, respirations 20. Blood pressure 140/50.

Digital compression of the right common carotid artery for several minutes did not produce any untoward symptoms or evidence of cerebral anemia.

*Indication for Ligation*—Repeated, copious, and uncontrollable hemorrhages from the right upper alveolus and cheek.

*Operative Procedure*—Under local infiltration anesthesia, the right common carotid artery was exposed by an incision anterior to the lower third of the sternomastoid muscle. The carotid sheath was incised and stripped from the artery a distance of 1 cm. The vagus nerve was identified and protected. A rubber covered Crile clamp was placed around the artery and the blades compressed until the flow of blood was stopped. Patient experienced no untoward symptoms. No 2 chromic catgut sutures were placed around the artery, one above and one below the clamp, and the wound packed with iodoform gauze. He was returned to the ward in good condition. About three hours later he was given a transfusion of 500 cc of blood, and 30 minutes after this transfusion a very large hemorrhage occurred from the mouth, the patient losing 2,000 cc of blood (measured) before bleeding was controlled by gauze pressure packing. The patient immediately became unconscious. Continuous intravenous saline was started and two citrate transfusions, one of 500 cc and another of 700 cc, were given.

The next morning the Crile clamp was removed and the ligatures tied. About this time paralysis of the left arm and leg was noted and patient became incontinent and

coma deepened. In the afternoon his pupils became dilated, fixed, and some slight voluntary movement was noted in the left arm. However, without further bleeding, patient's temperature began to rise, he developed cyanosis, irregular breathing, and he was given oxygen without improvement. His temperature rapidly rose to 109° F and he died.

*Course*—Ligation, transfusion, hemorrhage, lowered blood pressure, cerebral anemia, hemiplegia, death. *Final Diagnosis* Angioma arteriole recemosum.

**Case 20**—G B, male, age 31, was admitted to Memorial Hospital Clinic November 2, 1928. Eighteen months before admission he had himself noted that his left eye was slightly prominent and that there was some swelling of the eyelids. This unilateral protrusion became progressively more noticeable and in September, 1927, he noted blurring of vision. This was shortly followed by complete amblyopia of the left eye. At this time in spite of a negative Wassermann he was given salvarsan test therapy without any influence on the tumor growth. Several physicians had attributed his condition to focal

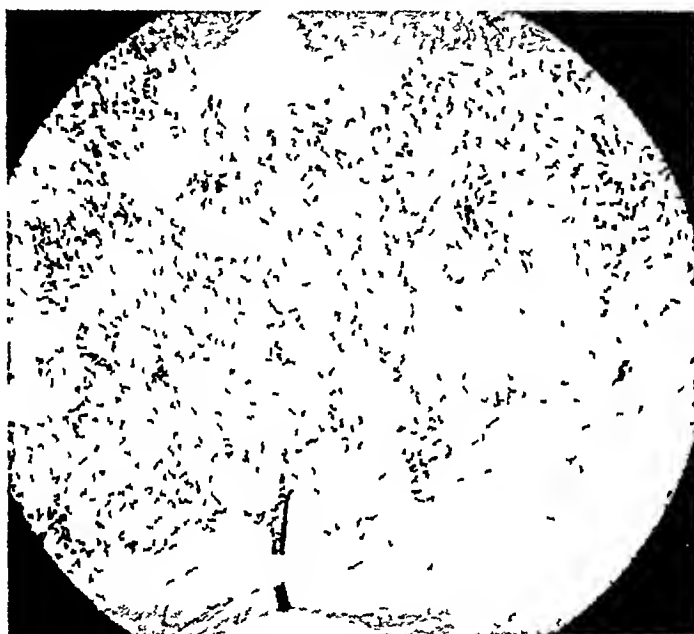


FIG 8—Case 20. Photomicrograph showing organizing thrombus in the internal carotid artery seven days after ligation of the common carotid artery of that side.

infection, and in November, 1927, a tonsillectomy was performed and, in February, 1928, he had treatment for sinus trouble. October 15, 1928, at the Cornell Clinic, a Kronlein operation was performed (this consists in the temporary resection of the outer border of the orbit in order to afford access to a retrobulbar orbital tumor). One week later an exenteration of the orbit was performed and the tissue removed was diagnosed as a cavernous hemangioma. The patient had always been in excellent health. His average weight had been maintained and his right eye had been normal.

*Examination*—On admission, November 2, 1928. The wound of the left orbit was partially healed. There was still a deep cavity about 1½ cm in diameter near the inner canthus, the base of which was lined by infected granulation tissue. There was considerable puffiness and edema of the tissues about the external canthus, but no evidence of residual tumor. General physical examination was negative.

He was given postoperative radiation consisting in the application of two brass filtered radium trays given a week apart each for a total of 2,000 mc hours. The wound healed completely and patient remained free of disease for a period of about three years.

In February, 1932, a new area of cavernous angioma was noted in the left cheek and tonsillar region, and four months later a large area measuring 4x3 cm was noted

in the region of the left temple. This area was treated by another radium tray for 2,200 mc hours. Roentgenograms taken at that time showed a cloudy left antrum with ill-defined walls and changes in the density of the bony structures of the orbit. The tumor was not controlled and gold filtered radon seeds for a total of 8 mc were inserted and followed by moderate radium reaction and considerable regression.

A year later there was renewed activity of disease in the temporal region and gold seeds were again inserted, this time for a total of 13 mc, followed by a marked radium reaction and very little regression of disease. In June, 1934, an extension of disease was detected in the soft tissues of the left cheek and gold filtered radon seeds, for a total of 11 mc, were inserted. Six months later the same area required treatment, and 10 mc of gold seeds were inserted.

By May, 1936, disease appeared in the nasopharynx causing partial obstruction of the nares. Three months later a soft mass of tumor tissue became noticeable in the left



FIG 9—Case 20 (Cavernous angioma of orbit, soft palate, nasopharynx and cheek). Moderate tumor regression followed ligation of the left common carotid artery.

hard palate. Stereoscopic roentgenograms of the antra at this time revealed the presence of a destructive process involving the four walls of the left orbit, frontal sinus, left antrum and zygomatic arch. Disease in these areas progressed rather slowly and was not influenced by the intra-oral injection of 5 per cent sodium morrhuate. By October, 1937, the intra-oral disease had reached such an extent as to completely occlude the nasopharynx. The cheek portion of the tumor protruded between the teeth to such an extent as to prevent adequate mastication and a traumatic ulcer occurred. At this point, interstitial radium for a total of 36 mc was inserted into the soft palate in the hope of opening a passageway through the nasopharynx.

*Indication for Ligation*—Digital compression of the left common carotid artery against the cervical vertebra, sufficient to cause cessation of pulsation of the temporal artery, did not cause the patient any discomfort, dizziness, or other cerebral symptoms,

and it was decided as all other therapeutic measures had proven unsuccessful, that a common carotid artery ligation be carried out in a final attempt to bring about growth restraint in the tumor

*Operative Procedure*—Under local infiltration anesthesia, the common carotid artery of the left side was exposed below the level of the omohyoid muscle, the carotid sheath was incised and a rubber covered Crile clamp placed around the vessel and closed. Patient had no cerebral symptoms, and untied ligatures of No. 2 chromic catgut were placed above and below the clamp and the wound packed open. Patient had no untoward symptoms. Neurologic examination was negative. Twenty-four hours after the operation the packing was removed from the wound and the ligatures tied and the clamp removed. Blood pressure before operation was 150/120 and remained practically the same after operation.

A week after the first procedure, the left carotid bulb was exposed under local infiltration anesthesia and the common carotid artery, the bulb, the external and the internal arteries were found to be completely thrombosed. The external carotid artery was, however, ligated and a section for histologic examination was removed from the internal carotid artery. This section showed an organized thrombus (Fig. 8).

The postoperative course has been uneventful. The wound healed kindly and there has been slight regression of disease (Fig. 9). Patient is back at work.

An analysis of the 20 cases in which the common carotid artery was ligated at Memorial Hospital during the years 1926–1937, shows there were 17 males and three females. The average age was 50, the youngest was a male, age 27, and the oldest, a female, age 69. The left carotid artery was ligated in 13 cases and the right in seven cases. In ten instances a modified Crile clamp was applied for periods varying from 20 minutes to 48 hours. Seven of these patients died between six and 120 hours postoperative. An eighth patient died two and one-half months after operation, as the result of an infected thrombus in the common carotid artery (Table I).

An analysis of the immediate postoperative results reveals the fact that 11 patients died within five days of the operation (Table II). In seven of the postoperative deaths, the Crile clamp had been used and in four instances an immediate ligation had been performed. In six of these cases, death was preceded by the development of a hemiplegia, and in five cases the Crile clamp had been used. The five youngest patients in the entire series are included in this fatal group.

In this series, 11 patients (55 per cent) died within five days of operation and nine patients (45 per cent) recovered. Two patients survived the immediate hazards of common carotid ligation only to die at a later date after developing sudden dyspnea, *etc.*, one was two and one-half months postoperative and the other, three months postoperative. In one of these cases, the cause of death was undoubtedly an infected thrombus from the ligated artery, as a slight purulent discharge from the neck wound persisted up to the day of sudden death.

One patient is lost to follow-up, without evidence of disease one and one-half years postoperative. One patient is alive, with recurrent cancer, three months postoperative. One is alive five years without evidence of disease. One is alive and well four months, and another alive and well one month.

TABLE I  
SUMMARY OF 20 CASES OF LIGATION OF THE COMMON CAROTID ARTERY

Case No	Age	Sex	Diagnosis	Indication for Ligation	Method of Ligation		Hemiplegia	Result
					Immediate	Gradual		
1 G T	46	M	Cancer of buccal mucosa	Threatened hemorrhage	Immediate	—	No	Death 36 hrs after operation
2 J N	59	M	Cancer of anterior floor of mouth Cervical metastases	Hemorrhage	Immediate	—	No	Sudden coma, generalized convulsions and death 2½ mos after operation
3 J C	53	M	Cancer upper alveolus Cervical metastases	Threatened hemorrhage	—	Crile clamp— 24 hrs	72 hrs p o	Coma and death 5 days after operation
4 N W F	34	M	Cancer buccal mucosa Cervical metastases	Hemorrhage	Immediate	—	24 hrs p o	Coma and death 3 days after operation
5 D S	54	M	Cancer of tonsil Cervical metastases	Hemorrhage	Immediate	—	No	Died of cancer 2 yrs after operation
6 J B	63	M	Cancer of lower alveolus	Threatened hemorrhage	Immediate	—	No	Death 24 hrs after operation
7 C H	42	M	Cancer buccal mucosa Cervical metastases	Tumor invasion at operation	Immediate	—	No	Death 6 mos after operation from hemorrhage
8 H L	40	M	Cancer base of tongue	Tumor invasion at operation	—	Crile clamp— 30 min	72 hrs p o	Death 3 days after operation (Edema of brain)
9 C Z	45	M	Cancer hard palate Cervical metastases	Hemorrhage	—	Crile clamp— closed slowly	No	Died 5 days after operation (Edema of brain)
10 H K	56	M	Cancer of tongue, post-operative Cervical metastases	Tumor invasion at operation	Immediate	—	No	Immediate death

# LIGATURE OF COMMON CAROTID ARTERY

		tastases	tion						
11	50	M	Cancer of tonsil	Cervi-	Tumor inva-	—	5 min	No	Alive and well 5 yrs
B Z			cal metastases	tion	tion				
12	69	F	Cancer of tonsil	Cervi-	Threatened	—	Crile clamp—	24 hrs p o	Death 24 hrs after operation
C S			cal metastases		hemorrhage		5 hrs		(Softening of brain)
13	53	M	Cancer of larynx	Cer-	Threatened	—	Crile clamp—	36 hrs p o	Died 84 hrs after operation
G A			vical metastases		hemorrhage		36 hrs		(Thrombosis of common ca- rotid artery)
14	60	F	Cancer of thyroid		Tumor inva-	—	Digital pressure—	No	Lost to follow-up No evi-
L S					tion at opera-		5 min		dence of disease 1½ yrs after operation
15	60	M	Cancer buccal mucosa		Threatened	—	Crile clamp—	Spastic	Cyanosis and death 6 hrs
L U			Cervical metastases		hemorrhage		6 hrs		after operation
16	50	M	Cancer of lip	Cervical	Threatened	—	Crile clamp—	No	Sudden unconsciousness, dysp-
H S			metastases		hemorrhage		48 hrs		nea, cyanosis and death 3 mos after operation (Embo- lus?)
17	56	F	Cancer skin of face	Cer-	Hemorrhage	—	Digital pressure—	Partial—	Recovered Alive with disease
J R			vical metastases				few min	temporary	—4 mos
18	48	M	Carotid body tumor		Tumor inva-	—	Crile clamp—	No	Alive and well—4 mos
W M					tion at opera-		20 min		
19	27	M	Angioma arteriole race-		Repeated	—	Crile clamp—	24 hrs p o	Died of hemorrhage and cere-
M R			mosum (a partial tumor)		hemorrhages		24 hrs		bral anemia 30 hrs after op- eration
20	41	M	Cavernous angioma of		Growth re-	—	Crile clamp—	No	Alive 3 mos after operation
G B			orbit, nasopharynx, soft		strant		24 hrs		Slight regression of disease
			palate and cheek						



TABLE II  
ANALYSIS OF 11 DEATHS OCCURRING WITHIN FIVE DAYS POSTOPERATIVELY

Site of Ligation		DEATHS						Autopsy Findings
Case	Side	Anesthesia	Indication for Ligation	Wound Infection	Number Hours After Complete Artery Occlusion	Number Hours After Operation	Convulsions or Hemiplegia	
1 G T	Left	Novocain	Threatened hemorrhage	No	36 hrs	36 hrs	No	No autopsy
2 J C	Left	Novocain	Threatened hemorrhage	Cellulitis at time of operation	96 hrs	120 hrs	Right hemiplegia	No autopsy
3 W F	Left	Novocain	Hemorrhage	Cellulitis at time of operation	72 hrs	72 hrs	Right hemiplegia	No autopsy
4 J B	Left	Novocain	Threatened hemorrhage	Cellulitis at time of operation	24 hrs	24 hrs	No	No autopsy
5 H L	Right	Novocain	Tumor invasion at operation	No	72 hrs	72 hrs	Left hemiplegia	Edema of larynx edema of brain lobar pneumonia acute pleuritis septae spleen and polyserositis
6 C 7	Left	Novocain	Hemorrhage	Preoperative cellulitis of neck	120 hrs	120 hrs	No	Cancer of left superior maxilla radiation slough left side of neck bronchopneumonia edema of lung and meninges septae spleen
7 H K	Right	Gas oxygen and ether	Tumor invasion at operation	No	Immediate	At operation	No	No autopsy
8 C S	Left	Novocain	Threatened hemorrhage	Preoperative cellulitis of neck	19 hrs	24 hrs	Right hemiplegia	Softening and ischemia of entire left cerebral hemisphere—most marked in parietal area and precentral and postcentral gyri
9 G A	Right	Novocain	Threatened hemorrhage	Preoperative cellulitis of neck	48 hrs	84 hrs	Left hemiplegia	Metastatic cancer right cerebelle nodes radiation ulcer thrombosis common carotid artery pneumonia generalized arteriosclerosis
10 L Y	Right	Novocain	Threatened hemorrhage	Preoperative cellulitis of neck	Immediate	6 hrs	Spastic	No autopsy
11 M R	Right	Novocain	Repeated hemorrhage	No	6 hrs	30 hrs	Left hemiplegia	No autopsy

TABLE II—Eleven patients died within a period of five days after operation In seven cases cerebral complications were a terminal factor

postoperative Two patients died of cancer, one six months and the other two years after operation There were six patients in which it was necessary to remove the common carotid artery at operation, and four of these (66 per cent) made uneventful recoveries From this it would seem that immediate excision of the common carotid artery is less dangerous than simple ligation of the same vessel Excision probably removes to a certain extent the danger of thrombosis and embolism

We know that postligation thrombosis of the terminal portion of the common carotid artery and its branches occurred in at least two other cases, one, a patient, age 55, died 84 hours postoperative, and an infected arterial thrombus was found at necropsy, the other, a patient, age 41, developed postligation thrombosis extending throughout the common carotid artery as well as its branches Proof of this was obtained by a second operation, seven days after the first, at which time a section of the thrombosed internal carotid artery was removed for microscopic study In both these cases a Crile clamp was used We have no definite data on the frequency of this complication due to the limited number of our cases, the small number of autopsies permitted, and the fact that one dislikes performing a second operation upon a well patient merely for scientific information

The most frequent cause of death following common carotid artery ligation is one form or another of cerebral complication, eight patients in this series developed hemiplegia, one developed convulsions That is, 70 per cent of those who died showed definite signs of cerebral involvement Only five autopsies were obtained, and in but three cases was permission granted for brain examination In each of these three cases edema, softening or other gross cerebral changes were noted Two patients definitely died of embolus from an infected carotid artery stump One died of hemorrhage from the ligated end of the carotid, and in several cases edema of the glottis was a factor in the sudden death of the patient

#### SUMMARY AND CONCLUSIONS

(1) These facts seem to indicate that in patients with cancer, ligation of the common carotid artery as an emergency procedure is hazardous The operative mortality in our series of 20 cases was 55 per cent Frequent variations and abnormalities in the anatomy of the arteries of the neck and brain suggest that these gross anatomic anomalies may largely explain the variety of cerebral complications occurring after common carotid artery ligation

(2) Collateral circulation outside the cranium is probably of little significance after common carotid artery ligation

(3) The use of the Crile clamp for gradual occlusion of the common carotid artery does not improve the prognosis

(4) Age is apparently not a significant factor in prognosis The five youngest patients in this series died postoperatively Six of the nine (66 per cent) patients who recovered were over 50 years of age

(5) The most frequent cause of death (70 per cent) was a brain complication, while embolus, hemorrhage, and edema of the glottis are frequent factors in a fatal termination. Postligation thrombosis probably occurs quite frequently.

(6) Uncontrolled cancer, sepsis, debilitation, hemorrhage, dehydration and low blood pressure are factors influencing a fatal outcome following ligation of the common carotid artery, but the preexisting congenital blood vascular supply to the brain is an important factor, determining whether life can be maintained after one common carotid artery has been ligated.

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# THE LOCALIZATION OF INTRACRANIAL LESIONS\*

## THE DETERMINATION OF AREAS OF HYPERPATHIA OF THE SCALP

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REFERRED pain along the left arm in coronary spasm or occlusion is a well known symptom. Much more frequent than spontaneous pain, although not so commonly recognized, is a hypersensitive skin area in the first and second thoracic segments. Such zones are often spoken of in terms of hyperesthesia or hyperalgesia. However, this is not correct, for referred pain exhibits qualities of its own. Dragging the head or point of a pin over the skin causes an excessive, harassing pain to be suddenly experienced as soon as the pin approaches the skin area to which the pain is referred. This pain lasts longer than the causative irritation and tends to spread into adjacent, unstimulated areas. This phenomenon has been called "hyperpathia." The explanation given for its occurrence has been that painful stimuli, originating in internal organs, enter the posterior horns and change the character of sensations arising in skin and muscles of the corresponding spinal segments.

The determination of areas of hyperpathia, as outlined by Head,<sup>1</sup> proved, for many years, of great assistance in the diagnosis of duodenal ulcer, gall-bladder, appendix and kidney pathology, *etc*. Head refers, briefly, to two patients with brain tumors, one involving the choroid plexus, the other the cerebellum. The former showed a zone of hyperpathia over the forehead, the latter over the eyes and in the back of the neck. In this connection, Head mentions that pain to deep pressure over the head is related to the dura, superficial tenderness to the brain itself. He fails, however, to draw any conclusions from these two observations. Kocher<sup>2</sup> called attention to the traction pain from falx, tentorium and the blood sinuses, and also to the participation of trigeminal fibers running within the dura. Wilms,<sup>3</sup> Milner<sup>4</sup> and Vorschuetz<sup>5</sup> were the first to stress the importance of areas of hyperpathia of the scalp in the differential diagnosis of cranial injuries. Although Vorschuetz refers to brain lesions in the title of his article, all 12 of his patients suffered from fractures of the skull, most of them of the base. Consequently, the areas of hyperpathia were confined, in his patients, to the cervical segments.

We have determined the relationship of areas of hyperpathia of the scalp to the localization of intracranial tumors, abscesses, subdural hematoma, arachnoiditis and meningeal scar formations. Table I gives a survey of the type of lesions found in 100 patients, and Table II the location of the 79 tumors.

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The result of these examinations showed a correlation between the location of the area of skin hyperpathia and the accompanying intracranial lesion

TABLE I  
DISTRIBUTION OF INTRACRANIAL LESIONS IN  
100 PATIENTS WHO PRESENTED AREAS OF  
HYPERPATHIA OF THE SCALP

Tumors	79
Abscesses	6
Chronic subdural hematomata	4
Arachnoiditis	5
Scar formation	2
Negative	4
<hr/>	
Total	100

TABLE II  
LOCATION OF 79 INTRACRANIAL TUMORS

Frontal	23
Central	6
Parietal	12
Occipital	1
Temporal	9
Falx	2
Parasellar	10
Sphenoid	5
Cerebellar	7
Angle	3
Fourth ventricle	1
<hr/>	
Total	79

Figures 1 and 2 show the sites of the areas of hyperpathia as actually found in patients with tumors of the respective parts of the brain. The exact shape of the skin areas varies in different cases, and the relationship of the scalp zones to the underlying intracranial process is an approximate one. Although the area of hyperpathia does not represent the exact location of the tumor, it gives a sufficient indication of the region where the bone-flap should be turned down. Statistics show that the majority of brain tumors exhibiting areas of hyperpathia of the scalp were tumors above, at, or just below the surface of the brain, often involving the meninges directly or indirectly. One tumor, although deep seated, was accompanied by an area of hyperpathia. A possible explanation for this exception is that the middle cerebral artery was imbedded in the tumor.

In two types of tumors, those of the cerebellum and of the sphenoidal ridge, the localization could be outlined more accurately. The majority of the tumors of the posterior fossa affect, in some way, the cervical roots and cause a hyperpathia in C 2-4. However, deep-seated cerebellar tumors, producing traction on the tentorium, show, in addition or exclusively, a circular hyperpathia over the forehead or above the eyes, as described in Head's

patient In tumors of the sphenoidal ridge, a careful sensory examination, including electrical methods, may help in determining whether the first division of the fifth nerve is involved, that is, whether the tumor is confined to the lesser wing, or whether the lesion encroaches upon the second and third divisions in the neighborhood of the foramen rotundum and foramen ovale. Such a differentiation may change the surgical approach.

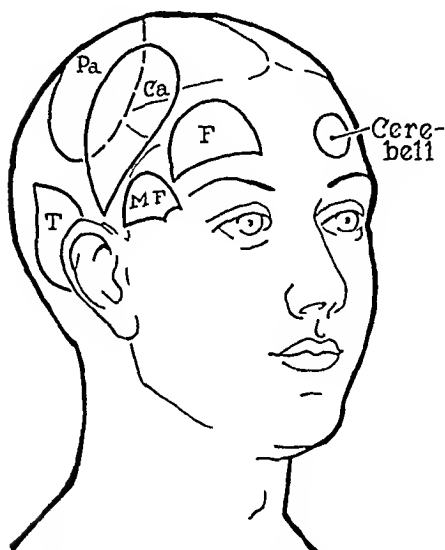


FIG 1.—Location of areas of hyperpathia on the scalp in processes of the frontal lobe (F), the central region (Ca), the parietal (Pa), and temporal lobe (T) including one group of angle tumors, and of the medial fossa (MF).

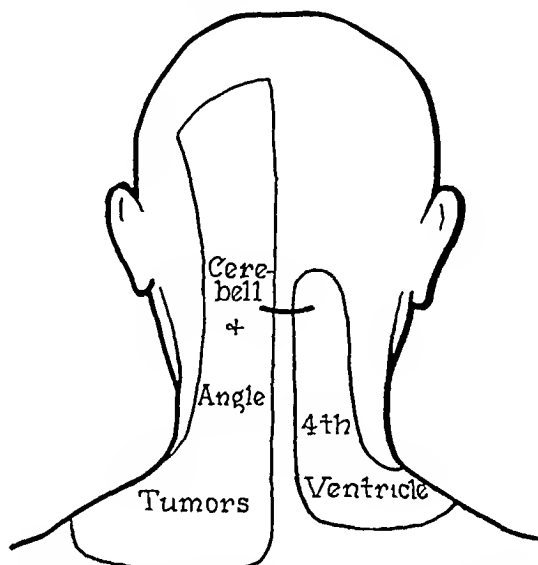


FIG 2.—Location of areas of hyperpathia of the scalp in processes of the posterior fossa and of the fourth ventricle.

Brief histories of six cases, herewith appended, may illustrate the specific field of application of this method.

### CASE REPORTS

**Case 1**—No 36136 M, male, age 62, was admitted to the hospital in stupor. He had had a vague history of headache and failing vision for some weeks, and showed increasing dulness and sleepiness. Examination revealed subnormal temperature, slow pulse, papilledema of 2D, and a questionable weakness of the left extremities. He had an area of hyperpathia over the right frontoparietal region. At operation an abscess was found in the indicated area.

**Case 2**—No 32917 C, male, aged 47, presented a peculiar picture. He seemed to have a tumor around the optic chiasm, possibly involving the corpus callosum and both frontal lobes, the left more than the right. He had a slight right facial weakness and bilateral exophthalmus, but the right eye bulged more than the left. There were 5D papilledema on either side. The area of hyperpathia pointed to the lower portion of the left frontal lobe. The ventriculogram suggested a right occipital tumor which was not found at operation. The autopsy revealed an extensive cystic glioma at the base of the left frontal lobe, which had destroyed the left corpus striatum and invaded the corpus callosum.

**Case 3**—No 29279 A, male, age 26, presented a problem of differential diagnosis between a sub- and a supratentorial tumor. Epileptic seizures of the prefrontal type, convergence reaction of the stretched arms and slight drop of the left arm, decrease of optic nystagmus at right gaze pointed to the right hemisphere, bilateral weakness of the

sixth nerve and weakness of the motor branch of the fifth nerve, a tendency to fall and to deviate to the left with closed eyes suggested a subtentorial lesion. The area of hyperpathia was situated above the right concha. Operation revealed an astrocytoma in the anterior portion of the right temporal lobe.

**Case 4**—No 30771 F, female, age 34, had noticed a gradually increasing exophthalmus of the left eye and a swelling over the left zygoma for five months. The distribution of the area of hyperpathia in the face (Fig 3), within which the time excitability of touch and pain points was increased in comparison with the opposite side, indicated a tumor originating from the lesser wing of the sphenoid. The tumor, an osteoma, which had its origin from the most lateral part of the lesser sphenoidal wing, had perforated the roof of the orbit and pressed upon the orbital fissure.

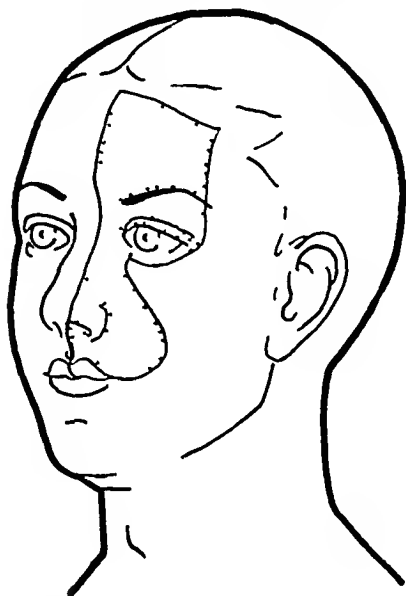


FIG 3—Location of area of hyperpathia chiefly in the distribution of the first division of the fifth nerve in a tumor of the lesser sphenoidal wing.

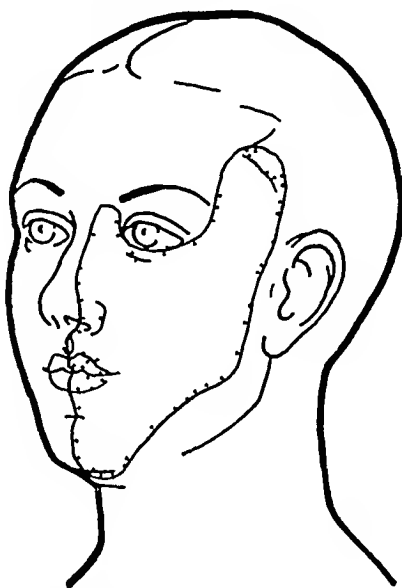


FIG 4—Location of area of hyperpathia in the distribution of the second and third divisions of the fifth nerve in a parasellar tumor, involving the region of the foramen ovale and rotundum and covering the greater sphenoidal wing.

**Case 5**—No 37199 L, male, age 25, showed exophthalmus of the left eye, and weakness of the seventh and twelfth nerves. Hyperpathia was found in the distribution of the second and third divisions of the fifth nerve (Fig 4). Touch and pain points were not diminished in number, and showed a normal threshold but increased time irritability. A tumor of the greater wing of the sphenoid, involving the region of the foramen rotundum and foramen ovale, was suspected. Operation revealed a parasellar meningioma covering the greater wing of the sphenoid.

**Case 6**—No 30835 McC, male, age 56, represents one of the cases which is listed as negative. He presented a slowly progressing paresis of the right side of the body with left-sided hemianopsia. The neurologic diagnosis was a right-sided fibroblastoma with signs of contrecoup. No area of hyperpathia was demonstrable. No tumor was found at operation. The later development stressed the probability of a thrombosis.

**COMMENT**—With the exception of the lower occipital areas, the pain seems to be referred to the skin over the distribution of the fifth nerve. Its ophthalmic branch supplies the dura over the convexity of the hemispheres and at the base of the anterior fossa as well as the falx by way of the ethmoidal filaments and the recurrent ramus of the tentorial nerve (McNaughton<sup>6</sup>). The recurrent branch of the first division provides the tentorium and its venous



sinuses The recurrent ramus of the second, and the spinal ramus of the third division innervate the dura at the base of the medial fossa The anatomic data explain the specific arrangement of the areas of hyperpathia, not the least why cerebellar tumors next to the tentorium have their skin representation over the forehead There is, furthermore, an uncertain factor in the part played by the vascular sensibility in the appearance of areas of hyperpathia

Penfield,<sup>7</sup> and Penfield and Norcross<sup>8</sup> outlined areas of referred pain on the scalp by stimulating the dural sinuses, the middle meningeal artery or its branches and some places low in the temporal and frontal lobes Fay<sup>9</sup> delineated areas of referred pain in the face by electric stimulation of the carotid artery and its branches near its bifurcation

### CONCLUSIONS

The determination of areas of hyperpathia of the scalp is a simple and helpful diagnostic method in localizing intracranial processes Of course, its value should not be overestimated It is not intended to replace any of the recognized procedures of a thorough neurologic examination However, it is a great aid in comatose conditions and gives an additional confirmation to the clinical diagnosis when present, a warning when absent

This is equally true in tumors, abscesses, chronic subdural hematomata, arachnoiditis, and meningeal scar formations, insofar as they are situated above, at or just below the brain surface

The correlation between the areas of hyperpathia and the locus of the intracranial lesions is very good in some cases, approximate in others

A diagram is given showing the site of the areas of hyperpathia, found in intracranial processes of different location

The method is of special value in the differential diagnosis of supra- and infratentorial tumors, in the finer localization of cerebellar and sphenoid ridge tumors, and in the differentiation between neoplasms and vascular processes

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# SPINAL SUBARACHNOID INJECTION OF ABSOLUTE ALCOHOL FOR THE RELIEF OF INTRACTABLE PAIN\*

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IN 1931, Dogliotti<sup>1</sup> reported that pain, produced by a great variety of pathologic states, could be relieved by the spinal subarachnoid injection of absolute ethyl alcohol. This form of therapy was shown to be particularly applicable to pain referred to the lower extremities and the lower half of the trunk. Alcohol was chosen as the therapeutic agent since its specific gravity permitted the operator to "layer" it on the upper surface of the cerebrospinal fluid within the spinal subarachnoid space. With a single injection one could, thereby, physiologically interrupt a relatively large number of spinal nerve roots and to a degree control the narcotizing effect by varying the quantity of alcohol introduced. The method seemed to merit a trial, since yearly, approximately 25 patients with metastatic malignant disease of the vertebral column associated with unrelenting pain were admitted to the Kings County Hospital for treatment. During the ensuing years (1932 to 1935, inclusive) 38 such patients were treated by the injection of alcohol into the spinal subarachnoid space, using variable quantities and different concentrations of the drug. No well systematized records were kept as to the exact changes in the motor and sensory functions produced, nor as to just how long these changes persisted following the alcohol injection. Since it was evident that our results were not as favorable as those reported by others (Stern,<sup>2</sup> Yeomans,<sup>3</sup> Saltzstein,<sup>4</sup> Dunphy and Alt,<sup>5</sup> Greenhill and Schmitz<sup>6</sup> and Abbott<sup>7</sup>), it was decided to study in detail a series of patients thus treated.

From July, 1935, to July, 1936, 18 patients were selected, all of whom complained of pain about the lower abdomen, hips, buttocks or down the lower extremities as a result of metastatic malignant disease. Neurologic examinations were carried out before the alcohol was injected, immediately after the completion of the injection, three hours later, at the end of 24 hours and thereafter according to the changes produced by the alcohol. Two positions for injection were used, one in which the sacral area was the highest point of the spinal axis, and a second in which the spinal column was laterally flexed in such a manner that the cervical and sacral regions were kept well below the site of the injection. In no instance in this series was

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the alcohol introduced at a level higher than the twelfth thoracic vertebral interspace. Since two positions for injection were employed and since significant neurologic and therapeutic disparities relative to each were noted, the technic and the results will be presented separately.

The first 12 patients in this series were treated by the method in which the lumbosacral region was placed at a higher level than the site of the injection. The distribution of the pain suggested that it would be necessary to bring the alcohol in contact with the lower lumbar and the sacral spinal roots and, furthermore, we were considerably influenced in the choice of

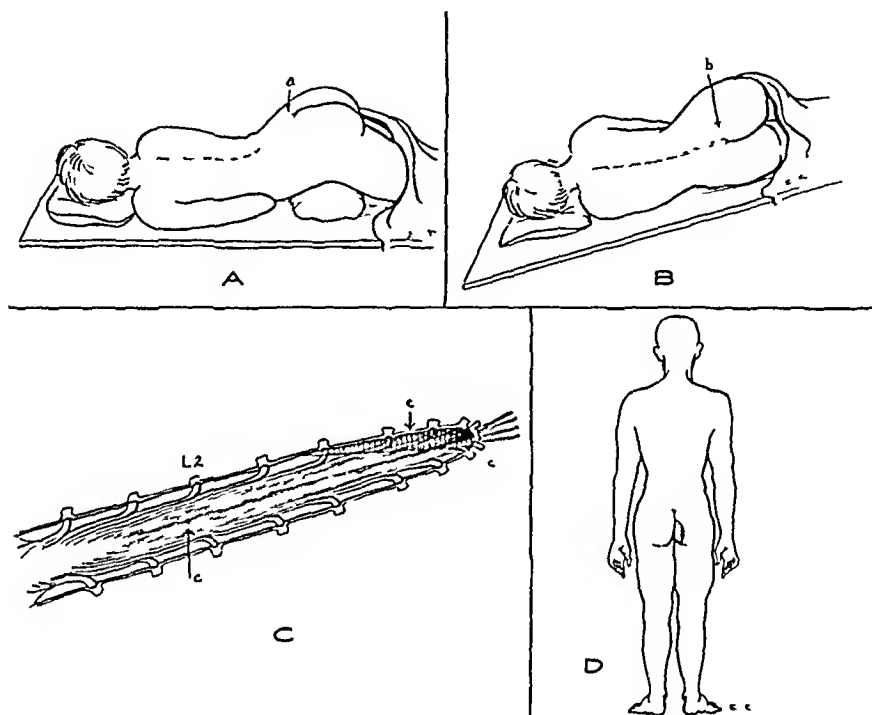


FIG. 1.—(A) Illustrating the position used by Greenhill and Schmitz in which the lumbosacral area (a) was sharply elevated by a pad. (B) Position for injection described in text as Method I, the coccygeal region (b) being the highest point of the spinal axis. (C) Author's concept of the level to which the alcohol rises following an injection into the subarachnoid space at the second lumbar vertebral interspace (c). (D) Illustrating the zone of cutaneous anesthesia produced by the injection of 1 cc of absolute ethyl alcohol with the patient in position B.

this method by the results reported by Greenhill and Schmitz,<sup>6</sup> who advocated the elevation of the hips at the time of the injection (Fig. 1-A). The details of this technic follow and will be referred to as Method I.

*Method I*—The patient is placed on a table with the painful side uppermost. The table is tilted to approximately 30° so that the coccygeal region is the highest point of the vertebral axis (Fig. 1-B). A spinal puncture is performed through one of the lumbar vertebral interspaces, the space selected varying with the distribution of the pain. One cubic centimeter of absolute ethyl alcohol is slowly injected in such a manner that one minute is required for the actual injection, care being taken not to inject air. The patient is left in the position of injection for 45 minutes and then kept flat in bed for

16 hours As an illustration of our experience with this method the following case is presented

**Case Report**—*Carcinoma of the Body of the Uterus Hysterectomy Roentgenotherapy Enlarged liver, jaundice No roentgenographic evidence of metastasis Pain over the right lumbosacral region, right hip, right groin and down the posterior aspect of the right thigh to the knee Subarachnoid injection of 1 cc of alcohol Immediate relief of pain with analgesia of skin zones supplied by the right spinal nerves S 4 and S 5 Persistent urinary and fecal incontinence Return of pain 40 hours after alcohol injection*

E G, female, age 53, had had a hysterectomy performed in August, 1935, for carcinoma of the body of the uterus Following the operation she was given a course of roentgenotherapy Four months later, in December, 1935, she was admitted to the Kings County Hospital, complaining of pain in the right lumbosacral region, right hip, right groin and down the posterior aspect of the right thigh to the knee The pain had been present for two months and had gradually increased in severity It was a dull, boring pain which varied in intensity and at the time of admission was totally incapacitating

*Physical Examination* disclosed a well developed, but poorly nourished, thin female, obviously in severe pain There was an icteric tinge to the sclerae, the liver edge was palpable 7 cm below the costal border but no intra-abdominal nodules were felt The abdominal wall was thin and relaxed There was a well healed suprapubic surgical scar Neurologic examination revealed no abnormal findings except for the absence of the abdominal reflexes

*Procedure*—The patient was placed on a table with the right side uppermost and the table was tilted to a 30° angle, elevating the lumbosacral region One cubic centimeter of absolute ethyl alcohol was injected into the thecal sac at the level of the second lumbar vertebral interspace Before one-half of the alcohol had been injected she experienced a burning sensation over the hip, thigh, leg and foot on the right side This sensation lasted about one minute, gradually fading to a warm glow Within two minutes after completion of the injection, she became aware of a numb feeling over the right lumbosacral region, right hip and the right thigh The relief from pain was instantaneous and quite dramatic

Immediate examination revealed analgesia over the cutaneous zones supplied by the spinal nerves S 4 and S 5 on the right side, without any other demonstrable neurologic changes (Fig 2) During the ensuing 24 hours, the patient had no pain but the urinary bladder became distended and required catheterization After 40 hours of relief, the original type of pain returned and continued in spite of large doses of opiates The analgesic and anesthetic zone as described persisted Overflow urinary incontinence and occasionally fecal incontinence continued until death, 11 days following the injection of alcohol

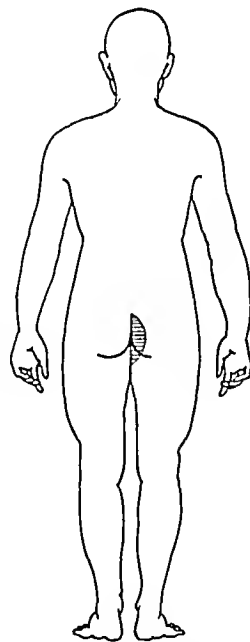


FIG 2—The zone of cutaneous analgesia produced in the illustrative case by the injection of 1 cc of alcohol by Method I (Right side uppermost)

*Comment*—Twelve patients were treated by this method, and the example presented here is, in general, representative of the results obtained Six of these patients had carcinoma of the cervix with local extension of the malignant process There was one case each of the following conditions Carcinoma of the body of the uterus with metastasis, carcinoma of the breast with metastasis to the spine, Hodgkin's disease involving principally the

lower retroperitoneal and pelvic lymph nodes, carcinoma of the left lung with metastasis to the lumbosacral spine, sarcoma of the ilium and lumbosacral spine and hypernephroma with metastasis to the spine. Eighteen injections were given by employing Method I. Eight patients received one injection each (two of these later received injections by Method II), two received two injections each, and two had three injections each. Four of the 12 patients were partially relieved of their pain for two weeks or less, five were benefited for approximately four weeks and two were improved for eight weeks. In all cases the relief was immediate, but in no instance was there complete relief of pain for a longer period than 24 hours. Nine of the 12 patients in this group had urinary retention with overflow incontinence as a result of the alcohol injection. Six of these had analgesia over the cutaneous zones supplied by spinal nerves S 4 and S 5 on the side uppermost at the time of the injection. In these six patients, the urinary bladder dysfunction persisted for from three to four weeks, whereas the remaining three who showed no loss of cutaneous sensation regained control of the urinary bladder in a week to 10 days. Two patients of this group required cordotomy, since the pain was not favorably influenced by repeated injections of alcohol.

Due to the obviously poor results obtained by the use of Method I and the frequency of the disturbing sphincteric complications, it was decided to try a method, the details of which follow and which will be referred to as Method II.

*Method II*—The patient is placed on a table in the lateral position with the affected side uppermost. A firm pad is placed beneath the lower thorax, thereby flexing the spine laterally as much as possible (Fig 3-A). The pad is placed in each individual case so that the apex of the scoliosis was three vertebrae above the site of the entrance into the spinal canal of those roots which are to be narcotized. The spinal puncture was performed through the twelfth thoracic, first, second, third or fourth lumbar vertebral interspace according to the distribution of the pain. A slow injection of 1.5 cc of absolute ethyl alcohol was given in such a manner that two minutes are required for the actual injection. The patient is left in the position of injection for 45 minutes and then kept flat in bed for 16 hours. As an illustration of our experience with this method the following case is presented.

**Case Report**—*Carcinoma of the Uterus. Roentgenotherapy and radium implantation. Pain in the lower lumbar region, right gluteal region and down the anteromedial aspect of the right thigh. Subarachnoid injection of 1.5 cc of absolute ethyl alcohol, right side uppermost. Immediate relief of pain. Persistent analgesia from T 11 to L 3 inclusive. Absent right knee jerk with weakness of the right lower extremity. Headache. Pain in the left sacro-iliac region and gluteal fold. Subarachnoid injection of 1.5 cc absolute ethyl alcohol, left side uppermost. Immediate relief of pain. Persistent analgesia from T 10 to L 3 inclusive. Absent left knee jerk with weakness of the left lower extremity. Recurrence of pain three and one-half months after injection.*

I. D., female, age 41, was admitted to the Kings County Hospital March 24, 1936. A diagnosis of carcinoma of the cervix had been established 16 months previously and

she was given roentgenotherapy and radiotherapy. Four months prior to the present admission the patient began to have pain over the lower lumbar spine, the right gluteal region and at times down the anteromedial aspect of the right thigh to the knee. The pain was described as dull, deep-seated and boring in character. For a short period, moderate relief from pain could be obtained by medicinal sedation, however, for two months just preceding admission, narcotics had failed to relieve the continuous pain.

*Physical Examination* revealed a well-developed, obese female, obviously in pain, but not acutely ill. Neurologic examination disclosed no abnormal findings. No roentgenographic evidence of metastases was demonstrable.

*Procedure*—The patient was placed on a table with the right side uppermost. A firm pad was placed beneath the left lower thorax in such a manner as to produce a

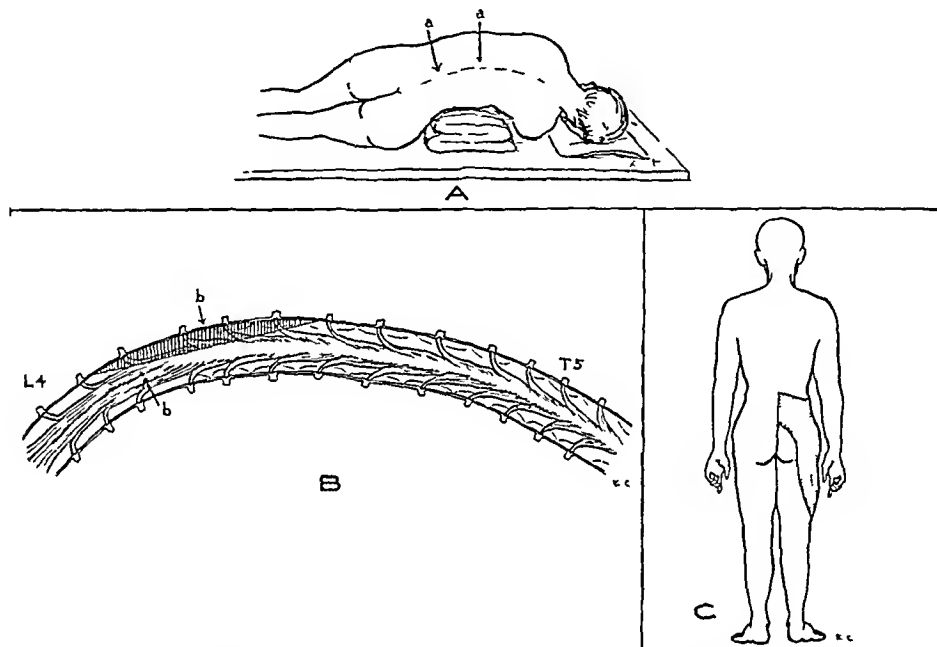


FIG 3—(A) Position for injection described in the text as Method II (a) site of the injection and (a') highest point of spinal axis (B) Author's concept of the zone of maximum concentration of alcohol (b) when introduced at (b') second lumbar vertebral interspace. The maximum effect of alcohol so introduced is halfway between the point of injection and the apex of the scoliosis (C) Average zone of cutaneous analgesia demonstrable following an injection of 1.5 cc of alcohol by Method II. The sacral area is not affected.

scoliosis with the apex of the curve at the posterior spinous process of the first lumbar vertebra. A slow injection of 1.5 cc of alcohol was given into the third lumbar vertebral interspace. The patient experienced a warm feeling over the anterolateral aspect of the uppermost thigh. This warm glow slowly spread downward to the ankle and upward to the site of the injection, then gradually subsided after three minutes, giving way to a "sleepy" sensation over the same area. The patient was left in the position of injection for 45 minutes and was then kept flat in bed for 16 hours.

Immediately following the injection an examination revealed an area of analgesia over the right side implicating the cutaneous zone supplied by spinal nerves T10 to L3 inclusive, an absence of the right knee jerk and a mild weakness of the right lower extremity. Appreciation of touch was blunted but not completely lost over any portion of the affected area. Within 15 minutes, there was a definite recession of both the upper and the lower levels of the analgesic zone, more marked, however, at the upper border of this area. Within 16 hours, the cutaneous analgesia had receded to the area supplied by spinal nerves L1, L2 and about one-half of L3 (Fig 4). There was no disturbance of function of the urinary bladder. Several hours after the injection the patient

inadvertently raised her head and immediately experienced a mild headache which lasted for three hours. On the day following the injection, she was able to walk about although there was some weakness of the right lower extremity. After 72 hours the right knee jerk could be obtained and she was discharged from the hospital free from pain. Seven days later she was readmitted, complaining of dull, persistent pain over the left sacro-iliac area extending over the left buttock. The pain was severe enough to disturb sleep and had been present for five days. There had been no recurrence of pain on the right side.

An examination at this time, 11 days after the first injection, failed to reveal any motor weakness of the right lower extremity and the cutaneous analgesic zone remained the same as on the day of discharge from the hospital. A second spinal subarachnoid injection of 15 cc of alcohol was given through the third lumbar interspace, with the left side uppermost and with the pad under the flank in such a position as to produce

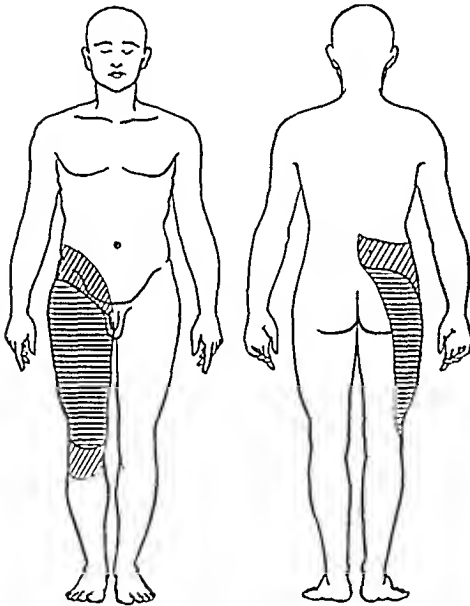


FIG 4—Illustrating the zone of cutaneous analgesia following an injection of 15 cc of alcohol by Method II (right side uppermost). Areas of recession indicated at either end of the analgesic zone.

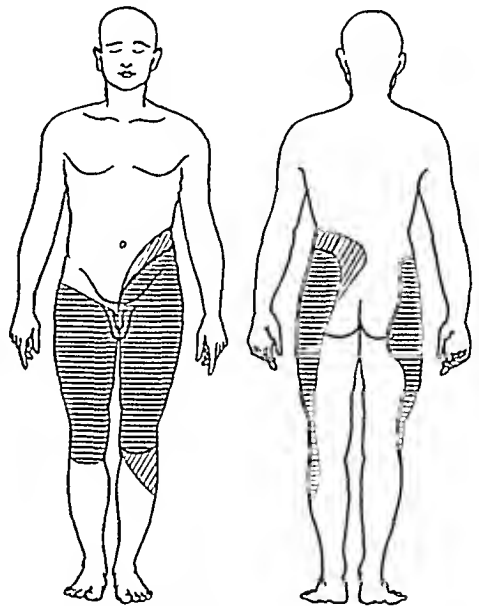


FIG 5—Illustrating the residual area of analgesia on the right side and the zone of analgesia on the left side produced by the second injection of 15 cc of alcohol. The areas of recession on the left side are indicated.

scoliosis with an apex at the posterior spinous process of the twelfth thoracic vertebra. After 0.7 cc of alcohol had been introduced, she complained of a burning sensation in the left foot which gradually rose to the left buttock but this disappeared in three minutes. Again the relief of pain was immediate. She was kept in this position for 45 minutes and then flat in bed for 16 hours. There was a mild headache for one hour.

Immediately after the injection, an examination revealed analgesia and diminution in the appreciation of touch over the cutaneous zone supplied by the left spinal nerves T 10 to L 3 inclusive (Fig 5), a mild weakness of the left lower extremity and an absence of the left knee jerk. Within 24 hours, the upper level of the analgesic area had receded two dermatomes and the motor weakness was not enough to interfere with walking. There was mild headache for five days following the injection. Six days after this injection the patient was discharged from the hospital free of pain and was able to walk with a slight limp, favoring the left side.

Four weeks after the injection for the left-sided pain and six weeks after the injection for the right-sided pain, she returned for reexamination. The areas of cutaneous

analgesia were found to be as illustrated in Fig 6 There had been no recurrence of the original pain and her only discomfort was an occasional "bearing down feeling in the rectum" The left knee jerk could now be elicited but this reflex was less brisk than the corresponding reflex on the right side and there was still a demonstrable weakness of the left lower extremity The patient remained pain-free for a period of three months after the last injection At the end of this time she had a recurrence of the original pain which persisted until her death, five and one-half months following the last injection

*Comment*—This case illustrates what may be accomplished by Method II A reinjection of alcohol would probably have been of value at the time of the recurrence of the pain but at this time the patient was not under our care

Eight patients were treated by Method II, however, two of these had been previously injected by Method I Two patients in the second group had carcinoma of the cervix and there was one each of the following conditions Carcinoma of the vulva with extension into the pelvis, carcinoma of the prostate with local recurrence, hypernephroma with metastasis to the pelvic bones and carcinoma of Bartholin's gland with extension into the pelvis Eight patients received 15 injections by Method II The dosage of alcohol used in eight injections was 1 cc, in one instance 2 cc and in the remaining six it was 1.5 cc One patient in this group was given three injections of alcohol (dose 1.5 cc) within a single month, and she was pain-free for only a total of 20 days of this 30-day period

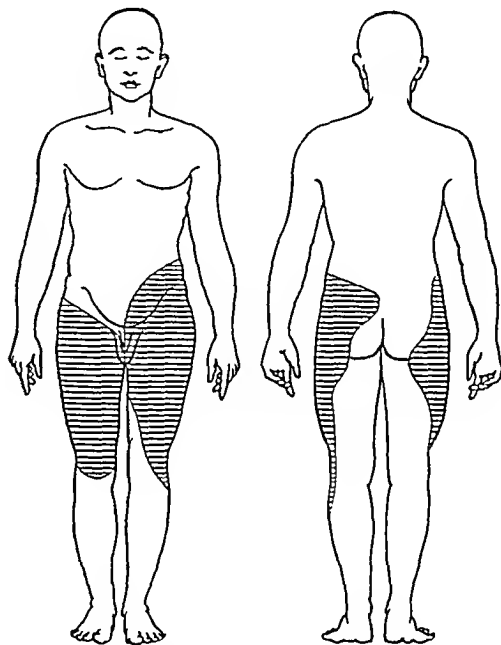


FIG 6—Illustrating the residual zones of cutaneous analgesia six weeks after the first injection of alcohol and four weeks after following the second injection

The best result in the group treated by Method II, was the case of I D used as the illustration for this method Four of these eight patients were pain-free for from one to three and one-half months, three had relief from pain for from seven to 15 days and one was comfortable for less than a week There was not a single instance of urinary bladder or rectal incontinence in this group of cases Changes in the deep reflexes were noted following six of the 15 injections and in three of these six instances, definite motor paresis of the affected lower extremity could be demonstrated In one case, this motor weakness persisted for one month Following 14 of the 15 injections given by Method II, cutaneous analgesic zones embracing two to nine dermatomes could be demonstrated This disturbance of appreciation of cutaneous stimuli (pain and temperature) was quite variable in its duration, lasting from a few hours in some to more than three months in other instances As recorded by Dunphy and Alt,<sup>7</sup>



the most complete relief from pain was noted in those cases in which the resultant analgesic zone corresponded to the distribution of the pain

*Discussion*—From time to time, a method for the control of pain has been advocated, which for a period retains a certain degree of popularity only to give way to newer and seemingly better procedures. Up to the present time, the outstanding measures have been (1) The administration of opium and its derivatives, (2) rhizotomy, (3) paravertebral injection of alcohol, (4) various operations upon the sympathetic nervous system, (5) cordotomy, and (6) spinal subarachnoid injection of alcohol. Each of these measures has merit when applied to properly selected cases but not infrequently results in failure if used indiscriminately. The opium derivatives are commonly employed and everyone is familiar with their progressive ineffectiveness, intradural section of the posterior spinal roots is often undesirable since a large number of roots must be divided to interrupt the wide-spread, pain-carrying pathways from a particular zone, paravertebral alcohol injection is technically difficult, painful, and is effective only in the hands of a few, sympathectomies and sympathetic ganglionectomies are unreliable from the standpoint of relief of pain except in a limited group of diseases, cordotomy is theoretically and practically the procedure of choice, provided that pain appears during the early course of the malignant disease, however, such an operative procedure is not infrequently contraindicated because many patients with malignant disorders have pain only during the terminal phase of their disease, lastly the spinal subarachnoid injection of alcohol is a procedure of simple execution but attended with dire results if improperly conducted. As has been stated, several authors have reported satisfactory relief from pain by employing this method, especially the constant boring pain associated with extension of malignant diseases about the lumbosacral plexus and the lumbar vertebral column. More recently, scattered case reports, as well as our observations, indicate that urinary and fecal incontinence is not an uncommon complication following this procedure. Tureen and Gitt<sup>9</sup> reported the occurrence of a "cauda equina syndrome" following the subarachnoid injection of alcohol and referred to a similar observation by Sloan<sup>10</sup>. The former authors described a patient with "sciatica" who had received an injection of 1 cc of absolute ethyl alcohol into the lumbar thecal sac with the hips in a sharply elevated position. The injection was followed by relief of pain for three weeks but the patient had urinary incontinence for six weeks (date of last examination). Sloan<sup>10</sup> described a somewhat similar experience with rectal and vesical sphincter paralysis that had persisted for eight months. Dogliotti<sup>8</sup> observed that when the sacral zone was placed at a higher level than the point of injection into the lumbar thecal sac, urinary incontinence frequently occurred. Stern<sup>2</sup> stated that "a transitory sensory paralysis of the bladder and rectum may occur with injections between the second and third lumbar spine. This can be avoided by limiting the dose at this level to 0.5 cc." Our experience differs from Stern's in that urinary incontinence was not encountered following five injections by Method II.

through the second lumbar interspace, using doses of 1, 1.5 and 2 cc. On the other hand, nine out of the 12 patients had urinary incontinence following the injection of absolute ethyl alcohol by Method I. Our results indicate that vesical and rectal sphincter disturbances are due to a position of the patient at the time of the injection which permits the alcohol, in a concentrated form, to reach the sacral subarachnoid culdesac, thereby affecting the sacral spinal roots on both sides (Fig. I-C). It is true that, most often, only unilateral disturbance of cutaneous sensation can be demonstrated following an injection by Method I (Fig. I-D), however, bilateral changes (analgesia of cutaneous areas supplied by spinal nerves S 3, S 4 and S 5) have been observed in two patients that were injected by this method (cases not included in this series). The observations following the 33 injections given in this series, lead us to believe that the site of the injection and the quantity of absolute ethyl alcohol used (not exceeding 2 cc.) plays a very minor rôle in the production of fecal and urinary incontinence and that this most disturbing complication can be easily avoided if the lumbosacral area is kept well below the level of the site of the injection (Fig. 3-A). In those instances in which it seems necessary to block the lower lumbar and the sacral spinal roots in order to relieve the pain and in which cordotomy is inadvisable, the patient should be warned that an attempt to relieve the pain by alcohol injection will probably result in urinary and fecal incontinence.

Following the injection of 1.5 cc. of alcohol under the conditions described in Method II, a wide zone of cutaneous analgesia (and in some instances also hypesthesia) appears within two minutes, but after 10 to 15 minutes the upper and lower margins of this zone will have receded from two to three dermatomes respectively. Usually this recession is greater at the upper border. For example, as in the case used to illustrate Method II, the residual demonstrable effect of the alcohol on the spinal nerve roots began at the level of the site of injection and extended cephalad three dermatomes from this point. This no doubt is due to the greater concentration of alcohol at this level and it is our belief that this narcotizing action of alcohol on spinal nerve filaments takes place within the arachnoid sleeve that is prolonged over the nerve roots. The fibers carrying pain and temperature are less well protected by myelin and consequently are more susceptible to the action of the alcohol. When a large dose (over 1.5 cc.) of alcohol is used, the concentration of the drug in the arachnoid sleeve is great enough to affect all of the dorsal root fibers and in some cases the motor roots as well. Diminution to absence of deep reflexes may be found on the affected side, however, impairment of motor function is seldom of sufficient degree to cause concern. These results indicate that the margin between the amount of absolute ethyl alcohol necessary to relieve pain and that which produces damage of the anterior spinal roots is very small.

Absolute ethyl alcohol introduced into the subarachnoid space produces a cellular reaction which may be as great as 2,500 cells per cubic millimeter of cerebrospinal fluid. There is usually an associated mild systemic febrile reaction which subsides in from 24 to 48 hours. Unless the patient is kept abso-

lutely flat in bed, as outlined under the description of the methods employed in this series, headache may be quite troublesome. When the indications for repeated injections are present, as for bilateral pain, the injections should be given one week apart. Relief of pain for two months should be considered a good result and in instances where the pain returns after an interval of freedom, a second injection is indicated.

### CONCLUSIONS

The spinal subarachnoid injection of absolute ethyl alcohol for the relief of pain is useful in properly selected cases. Only patients having incurable malignant disease should be subjected to this most capricious procedure. A careful analysis of the pain-carrying pathways involved in each patient must be made before attempting to relieve the pain by such an injection. Charts and diagrams available in standard textbooks are often helpful in determining the segments to be "blocked." The position of the patient at the time of the injection should be such that the alcohol will not affect the root filaments of the sacral spinal nerves. The quantity of alcohol used at a single injection should never be more than 2 cc and preferably not more than 1.5 cc. Injections of doses smaller than 1.5 cc should be tried until familiarity with the procedure has been gained. Records of the exact motor, sensory and the vesical and rectal sphincter changes produced by the alcohol should be kept for reference, when and if future injections are required.

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# RECURRING PERITONITIS FOLLOWING OPERATIVE REDUCTION OF A STRANGULATED INGUINAL HERNIA\*

CURE FOLLOWING RESECTION OF THE DAMAGED LOOP

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**Case Report**—H. S., male, age 39, was admitted to the service of Dr. Edward Crossan at the Episcopal Hospital March 3, 1936, with an incarcerated inguinal hernia of 36 hours' duration. For 17 years, he had had a right inguinal hernia which he had kept reduced by means of a truss. The onset of his present difficulty had been characterized by abdominal pains which awoke him the morning of the day before his admission. Vomiting soon followed and that evening he noticed a lump in the right inguinal region and the pain became most marked there. Gas was passed by rectum until six or eight hours before admission. On examination there was evidence of considerable fluid loss, rapid pulse and subnormal temperature. There was a tense, tender mass the size of a walnut in the region of the right inguinal canal. The abdomen was slightly distended and no borborygmus could be heard. Before taking the patient to the operating room, an intravenous infusion of 500 cc. of normal salt solution was given and a Jutte tube passed into his stomach.

**Operation**—March 3, 1936. Under local anesthesia, the inguinal canal was opened and a blue-black mass exposed. Constriction of this herniated tissue was found at the internal ring. Liberation was accomplished by incising the ring. The sac was then opened and found to contain a very short loop of blue-black ileum with a normal appearing mesentery. The surface of the gut had a distinct sheen. After liberating the intestine from all pressure and covering with gauze soaked in warm salt solution, there was a definite improvement in color, characterized by the appearance of light red streaks on the antimesenteric surface. This improvement continued, and after 20 minutes of repeated observations the appearance was so good that it was thought that complete return to normal would occur. Peristaltic waves were seen to pass up to this loop and in an irregular manner pass along it. The loop was then returned to the peritoneal cavity and the hernia repaired with catgut by the Ferguson technic after excising the sac and closing the peritoneal defect.

**Subsequent Course**—Recovery was characterized by a persistent fever of 101° to 102° F. for the first four days, during which time intravenous fluids and suction drainage of the stomach were employed. His wound healed by primary intention and he was discharged on the nineteenth day in good condition.

Following his discharge he had intermittent attacks of epigastric pain of fleeting nature. On the morning of August 1, 1936, a little less than five months after his discharge from the hospital, he had an attack of severe pain in the right lower quadrant of his abdomen with radiation through to the back. The pain was so severe that his doctor had to give him morphine for its relief. He then began vomiting whenever he attempted to eat anything. Two more attacks of severe pain followed and the abdomen became diffusely sore. He was sent to the hospital 36 hours after the onset of symptoms.

On admission, August 2, 1936, he was seen to be acutely ill and to be having considerable abdominal pain. There was slight distention of the lower part of the abdomen, particularly the right lower quadrant. There was no evidence of recurrence of the

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herma but there was a vague sense of a mass just medial to the inguinal scar. No peristalsis could be heard. Temperature, 100.1° F, pulse, 92, respirations, 26, white blood cells, 21,000. It was thought that he had a generalized peritonitis secondary to perforation of the loop of ileum which had previously been incarcerated in the hernial sac, that this had become adherent to the parietal peritoneum, and that some sudden peristaltic rush had injured its slightly abnormal wall, causing a perforation and thus giving rise to a peritonitis. Operation was performed at once.

*Second Operation*—Under spinal anesthesia, the abdominal cavity was entered through a transverse incision just medial to the inguinal scar. On entering the peritoneal cavity there was an escape of purulent fluid. A loop of distended ileum presented in the wound and was found to be partly obstructed by a band of dense adhesions extending from the cecum to the abdominal wall. The adhesions were divided and the loop examined for a possible perforation but nothing even suggesting one was found. A large piece of the omentum was found to be detached from the main portion except for a thin fibrous bar. This was excised. The cecum showed an acute inflammatory process with plaques of fibrinopurulent material over its mesenteric portion. The appendix was found to be atrophic and, although the tip was buried and could not be readily visualized, it seemed obvious that it was only secondarily inflamed and showed no evidence of being the source of the peritonitis. No cause for the peritonitis being found and the patient's condition being so poor, it was thought unwise to remove the partly buried appendix, drains were placed on either side of the cecum and the abdominal wall closed with interrupted through-and-through silkworm gut sutures after closure of the peritoneum up to the drains with a continuous catgut suture.

The postoperative period was marked by the development of a temporary fecal fistula and of a transient pelvic mass. Roentgenologic examination of the colon following a barium enema failed to reveal any abnormalities and the patient was discharged September 7, 1936, 36 days after operation, in good condition with a healed wound. It was my impression that the cecum had been the source of the trouble, and that a small gangrenous area had allowed passage of virulent organisms into the peritoneal cavity.

Following this discharge in September, he was quite well in every way until 5:00 A.M. of the day of his third admission to the hospital, October 24, 1936. At that time he was seized with severe pain in the left lower quadrant of his abdomen which radiated into his penis and caused him to faint. This pain persisted, notwithstanding an effectual enema, sedatives and the application of heat and of cold.

On admission to the hospital, eight hours after onset of symptoms, he appeared somewhat shocked. He was having considerable abdominal pain. The abdomen was tender throughout but mainly over the left half, which was rigid. No obliteration of liver dullness was noted. No borborygmus could be heard. There was a small defect at the site of the drainage in his transverse operative scar. No masses could be felt and nothing abnormal was noted on rectal examination. Temperature, 99° F, pulse, 110, white blood cells, 26,500, neutrophils, 92 per cent, blood pressure, 100/70. It seemed that he had a peritonitis or a mesenteric thrombosis. If he had peritonitis, it was thought to be a primary one, as it was considered that his appendix could be excluded as a possible source, from previous examination of it, a perforated diverticulum of the sigmoid seemed ruled out by the recently negative roentgenogram of the colon, and the physical findings were against a perforated peptic ulcer. It was, therefore, decided that operation was contraindicated.

*Subsequent Course*—He was sent to the ward, placed in a Fowler position, and treated with intravenous glucose, morphine, and withholding of everything by mouth. On the morning after admission he seemed much better and was having only a little abdominal pain, which, however, was accentuated by moving. Examination of the throat at this time revealed a fiery red soft palate and pharynx with fibrinopurulent plaques of exudate scattered all over it. This appearance was almost exactly similar to that of

the peritoneal surfaces at the time of the last operation. Examination of the abdomen showed persistence of the generalized tenderness and muscle spasm of slight degree and absence of peristalsis. It was thought that the patient had a pneumococcus infection of the throat and of the peritoneum and a laryngologic consultant corroborated our impression of the throat condition. On the second morning after admission, his general condition was slightly better. The throat showed less redness and very little exudate. The abdomen was still slightly distended and the impression was gained of the presence of some free peritoneal fluid. Rectal examination revealed tenderness and some thickening high up on the anterior wall. Believing that we were dealing with a pneumococcus peritonitis, aspiration of the peritoneal cavity was performed through a point just to the left of the midline and halfway between the umbilicus and the symphysis pubis, 1 cc of thin sanguinopurulent material was removed for culture, and immediately streaked on a blood agar plate and on slides.

The temperature had fallen from a high 102° F, on October 25, 1936, to a 100.8° F. The white blood cells had fallen to 9,850 with 80 per cent neutrophils, of which 26 were of the stab form. Improvement from this time on was progressive. The bacteriologic studies showed the throat organisms to be diphtheroids and *Streptococcus albus* (*Escherichia grunthali*) and the peritoneal fluid showed a colon bacillus. The abdomen cleared more rapidly than the throat, but both conditions were satisfactory by November 7, 1936, when he was discharged from the hospital, 14 days after admission.

He remained well until December 13, 1936, when, an hour after eating a midnight supper, he began having abdominal pain and became distended. An effectual enema gave him some relief but after this he passed no more flatus. The next day he had generalized abdominal soreness and was unable to retain anything by mouth. He was seen in consultation at noon and was then noted to appear quite sick, temperature, 99° F, pulse, 100. There was moderate abdominal distention. Borborygmus sounded normal over the suprapubic region but had a tinkling character over the right upper quadrant and was absent in the left upper quadrant. There was a slightly tender, indefinite mass in the right lower quadrant. There was no evidence of recurrence of his hernia. Rectal examination revealed an indefinitely outlined mass partly filling the pelvis, but nothing within the rectum.

On admission (fourth) to the hospital December 14, 1936, his temperature was 100° F, pulse, 120, respirations 20. Hb 85 per cent, red blood cells, 4,730,000, white blood cells, 7,850, neutrophils 90 per cent, lymphocytes, 10 per cent. It was thought that he had an incomplete intestinal obstruction due to adhesions between loops of intestine. The mass was thought to be intestinal. Wangenstein suction drainage of the stomach was started, as was a continuous intravenous drip of 5 per cent glucose in normal saline. The abdomen was kept covered with a large flaxseed poultice and morphine sulphate gr 1/6 with atropine sulph gr 1/150 were given every four hours.

The next day his general condition was little changed. The abdominal distention continued, there was persisting tenderness and the mass in the right para-umbilical region remained. Roentgenologic examination revealed distended loops of small intestine with fluid levels. It was felt that operation was urgently required in spite of the fact that his leukocyte count had fallen to 3,120 and neutrophils 87 per cent, with only 44 per cent segmented forms. His temperature was 102.2° F, pulse, 112, respirations, 24, and had it not been for a knowledge of his amazing recuperative powers the operation would have been undertaken with greater misgivings.

*Third Operation*—December 15, 1936. Under spinal anesthesia, a lower right rectus incision was made. A diffuse peritonitis was found, there was no free fluid present but there were marked reddening and thickening of the peritoneum. Coils of small intestine were adherent to one another and to the parietal peritoneum, the omentum was greatly thickened and indurated and attached to the mesentery, and at one point to the parietal peritoneum. These adhesions were readily separated by blunt dissection. One segment

of the ileum was considerably enlarged and acutely angulated in such a way that complete obstruction was produced. At the apex of the angle there was marked narrowing of the lumen due to fibrotic changes. Peristaltic waves were seen to pass through this area, although no lumen could be felt. All of the mesentery was greatly thickened and indurated. The appendix was found running down toward the midportion of the pelvis and although obviously not the cause of the peritonitis, it was removed. A small pocket of pus was found deep in the pelvis when some coils of intestine were freed. Due to the multiplicity of areas of obstruction it was decided to perform an enterostomy rather than attempt anything more radical in his present condition. This was effected, according to the Witzel technic in a distended loop of ileum well proximal to the main point of obstruction. The tube was sutured only to the intestinal wall, the loop being in contact with the parietal peritoneum. The peritoneum was closed down to the enterostomy tube with a continuous catgut suture, and the remaining abdominal wall closed with through-and-through sutures of fine wire tied over stitch tubing.

*Subsequent Course*—Convalescence was prolonged. Intravenous infusions, transfusion, and continuous suction drainage of the stomach were employed. On the fourth post-operative day his intravenous intake was pushed to nearly 6,000 cc of 5 per cent glucose in normal saline, with the result that the next day he presented all the signs of an overloaded circulation—cyanosis, bubbling rales throughout both lungs, dyspnea and engorgement of the superficial veins of his face, neck, and chest. His output had been only 3450 cc. The intravenous fluid was stopped for 12 hours and then he was given 2,000 cc of 10 per cent glucose in normal saline by slow drip. There followed marked diuresis and immediate disappearance of the signs of pulmonary edema. He began passing flatus on the fifth day, and the enterostomy tube was allowed to come out on the seventh. Recovery was uneventful after this, and he was discharged in good condition with all wounds healed, January 29, 1937, 45 days after his admission. Before discharge he had a complete gastro-intestinal series, which showed no evidence of disease except for slight dilatation of many loops of ileum, thought to be due to some slight constriction of the ileum in the region of the ileocecal valve. Culture of the pus found in the peritoneal cavity at operation showed a member of the colon group of intestinal flora.

The patient remained in excellent health until 4 00 A M April 19, 1937, when he was awakened by lower abdominal pain and a desire to defecate. His bowels did not move and he felt nauseated. The pain gradually increased in severity and involved the entire lower abdomen. He was admitted to the hospital at 10 30 A M. At this time he looked sick but not as badly as on previous admissions. The abdomen showed diffuse rigidity and tenderness with the greatest degree in the right lower quadrant where the musculature was the poorest. No borborygmus could be heard. Temperature, 100° F, pulse, 108, respirations, 20, white blood cells, 25,000, neutrophils, 92 per cent. Fluoroscopic examination showed no evidence of air under the diaphragm. *Diagnosis* Acute peritonitis.

Treatment was started with intravenous glucose infusion and suction drainage of the stomach, and administration of morphine. Three hours later the pain had become more severe and the tenderness more marked. There was present the sensation of intestinal loops being just under the skin in the right lower quadrant. Mesenteric embolism seemed a likely diagnosis, but in view of the findings at previous operations, a primary peritonitis was the diagnosis chosen.

*Fourth Operation*—Under spinal (neocaine 150 mg) anesthesia, the peritoneal cavity was entered through a transverse incision made through the scar of the previous similar incision. There was an escape of milky, purulent fluid which had a so-called *B coli* odor. There was a fibrinopurulent exudate on the peritoneal surfaces and many old adhesions between loops of small intestine and the parietal peritoneum. There was one very distended loop of ileum which was lying just over the cecum, and upon delivering

it out of the wound, it was seen that its mesentery was greatly thickened, and a definite, small perforation was found in the ileum at its mesenteric border. This opening resembled an acute peptic perforation, having a punched-out appearance and a zone of induration immediately surrounding it for about 1 cm. There was no evidence of abnormality of the mesenteric blood vessels, and no cause for the perforation was found. The perforation was closed by means of a purse string suture of linen, reenforced with interrupted Lembert sutures of fine silk and covered with a free transplant of omentum. Because of the distention in this loop of gut, an enterostomy, according to the Witzel technique, was performed, in order to prevent undue pressure on the sutured perforation. There was no evidence of obstruction, although this loop of gut was more distended and indurated than others. The abdominal wall was then closed with through-and-through sutures of silkworm gut around the enterostomy tube. Cultures of the peritoneal fluid were taken, which showed diphtheroids and bacilli from the intestinal tract, *Bacteroides variegatus*.

*Subsequent Course*—Intravenous administration of glucose and salt solution, and the use of suction drainage of the stomach were continued for the first few days, and he made slow but definite improvement. He then picked up more rapidly, the enterostomy tube was allowed to come out on the seventh day, and the wound healed without incident. He was discharged on the eighteenth day in good condition with his wound healed.

He continued to improve rapidly. A gastro-intestinal series revealed a constant narrowing of a portion of the terminal ileum with some dilatation of the intestine above. The picture resembled that seen in instances of regional ileitis. It was believed that all of his attacks had been due to repeated, minute perforations of this loop of ileum, which had probably been the loop of intestine originally incarcerated in the inguinal hernial sac and which had been so badly damaged that it had never returned to an entirely normal condition. Furthermore, it had become partly twisted upon itself, and at each operation this loop had been seen to be more prominent than any of the others, but at no time before had any suggestion of a perforation been seen. It was thought, therefore, that resection of this loop of intestine would be necessary to prevent further recurrences of his trouble, and he returned to the hospital, for his sixth admission, June 5, 1937, to have a resection of part of his ileum. Except for the scars of his previous operations and the resulting weakness of his abdominal wall, he was found to be in good condition.

*Fifth Operation*—June 7, 1937. Under nitrous oxide-ether anesthesia, the peritoneal cavity was entered after excision of the transverse operative scar. The loop of ileum which had previously given trouble was found to be reddened, diffusely thickened to a mild degree, with its mesentery greatly thickened and containing enlarged lymph nodes. There were numerous filmy adhesions to the omentum and other loops of intestines which were easily released. The diseased part of the ileum began about 18 inches above the ileocecal valve and extended approximately for about one foot. The intestine above and below this segment appeared to be normal. Accordingly, this entire segment was resected together with a wedge of the mesentery, and the continuity of the intestine restored by means of an end-to-end anastomosis. The abdominal wall was then closed with through-and-through sutures of silkworm gut, without drainage. Convalescence was uneventful and he was discharged on the fourteenth postoperative day, with his wound solidly healed and he in good general condition with normal bowel movements.

*Pathologic Examination*—*Gross*. The loop of resected gut showed nothing distinctive. There was a diffuse thickening of the wall and the site of the previous perforation could be determined by the small scar near the mesenteric border of one part. There was some thickening of the mesentery with moderate hyperplasia of the lymph nodes. *Microscopically*, there was the usual picture of reaction around a foreign body, in this case the linen suture used for the closure of the perforation. There was some



edema of the subserous layer of the wall of the ileum and some diffuse infiltration with fibroblasts, of the muscle layers

*Subsequent Course*—Improvement continued in every way and he had no further symptoms until September 4, 1937, when he noticed a bulging in his right inguinal region. He was seen in the Follow-Up Clinic, and it was obvious that he had a recurrence of his original hernia. A walnut-sized mass appeared at the external ring when he stood or strained and disappeared when he relaxed. He was readmitted to the hospital (seventh admission) September 9, 1937, for the repair of the recurrent hernia.

*Sixth Operation*—September 11, 1937. Under spinal anesthesia (neocaine 150 mg.), a definite sac was found extending halfway down the canal. High ligation of the sac was accomplished and the defect in the abdominal wall carefully repaired, with overlapping of the transversalis layer, using fine silk sutures. The rest of the repair was effected, according to the technic of Bassini, with the use of silk sutures. Recovery from this procedure was without incident and he was discharged on the thirteenth day after operation with wound healed by primary intention.

*End-Result*—It has now been just a year since this patient's discharge from the hospital following the removal of the diseased segment of ileum. He has been free from symptoms and has gained a great deal of weight and strength. Due to the number of abdominal operative scars he has worn a supportive belt but there have been no evidences of incisional hernia.

The course of events in this case seemed most confusing until the perforation in the ileum was discovered. The loop of intestine which became incarcerated in the hernial sac was so badly damaged that it did not return to its normal condition. It became attached by adhesions to the omentum and to the parietal peritoneum in such a way that partial obstruction in it was produced, and when the tension within it had become sufficiently great there was passage through its walls of intestinal organisms with the production of a peritonitis. On three occasions this leakage was not associated with any demonstrable perforation. During one of the three episodes, the patient was not operated upon, and it is reasonable to presume that the cessation of oral intake of fluid and food, and high immunity of the peritoneum, were sufficient to seal off the leaking area. The association of the acute pharyngitis apparently was coincidental. The remarkable recuperative powers demonstrated by this patient, and more specifically by the peritoneum, in handling heavy contamination without the supposed aid of direct drainage, except in the first attack of peritonitis, are of interest. The chief point raised for discussion in this case has to do with the handling of the doubtfully viable loop of gut found in incarcerated herniae. In this particular case, it seems most probable that had the loop not been returned to the peritoneal cavity but treated by exteriorization or even by resection, that this patient might have been saved all of the subsequent attacks of peritonitis. It was thought by the operator in this case that the viability of the loop had been well demonstrated, but this decision is one of great difficulty and must be based upon a broad experience. In view of the experience gained in this particular instance, it would seem wiser in the future to err on the side of radical treatment, rather than by conservatism to subject the patient to danger of subsequent serious illnesses.

# NONROTATION OF THE INTESTINE

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THE majority of abnormal positions of the intestines found in patients are due to disturbances in the normal embryonic development of the alimentary tract. Most abnormalities occur in the midgut, malpositions of the fore- and hindgut being extremely rare. The knowledge of the different conditions produced by anomalies of rotation of the midgut is not of mere theoretic interest but of considerable practical consequence. In order to understand anomalies of rotation it is necessary to understand the normal development.

*Embryology*—For practical purposes the alimentary tract is divided into the three parts already mentioned. The foregut, down to the papilla of Vater, which has mainly digestive functions, the midgut, from the middle of the duodenum to the middle of the transverse colon, which is mainly absorptive, and the hindgut that follows, which serves principally for excretion.

The most active part embryologically is the midgut. The axis of the midgut is formed by the superior mesenteric artery, from which it derives its blood supply, and which divides it in the pre-arterial segment containing the distal duodenum, the jejunum and proximal ileum, and the postarterial segment containing the distal part of the ileum and the proximal colon. At about the fourth week of embryonic development the comparatively small abdominal cavity becomes crowded with the enlarging liver and cannot longer accommodate the rapidly growing loop of the midgut. The greater part of this is pushed out together with a pouch of peritoneum into the elastic umbilical cord, thus forming the "physiologic umbilical hernia" which persists until the tenth week. The midgut, while contained in the umbilical hernia, turns 90 degrees around the axis of the superior mesenteric artery, from the sagittal to the frontal plane. This torsion is called the first stage of rotation. After completion of this stage the midgut is found suspended from the narrow duodenocolic isthmus. Essentially the same condition we find almost unchanged after birth in persons in which the rotation of the intestines came to a standstill at this point, the second and third stages having failed to follow.

At about the tenth week of development the return of the midgut into the peritoneal cavity and the second stage of rotation occur simultaneously. The theory is that a comparatively sudden expansion of the peritoneal cavity at this time creates a negative pressure, causing a suction that pulls back the extruded midgut. If the orifice of the physiologic umbilical hernia is of normal, relatively narrow size, it does not permit the simultaneous return of the

pre- and postarterial limbs of the midgut loop. The larger diameter of the proximal colon contained in the postarterial segment is held back until the narrower pre-arterial part has passed the opening. On account of other anatomic obstructions, such as the left umbilical vein, the pre-arterial intestine is turned aside in the process of its return and forced to rotate in a counter-clockwise direction around and behind the superior mesenteric artery and the postarterial colon. The completed second stage of rotation amounts to 180 degrees, first and second stages together to 270 degrees.

It is interesting to note that the second stage of rotation, which is the most important, takes place within a much shorter time than the two other stages of rotation. It happens so quickly that no specimens have ever been found in which it could be observed during its actual occurrence.

After the second stage of rotation is finished, the midgut is found to have completely reentered the abdominal cavity. The small intestine has crossed the mesocolon posteriorly and has rotated behind the proximal colon. The cecum is found immediately below the liver.

As the first stage of rotation is the preparation for the important second stage, the third stage represents its completion. It occurs between the eleventh week and some time after birth, and involves the final descent of the cecum and the final permanent fixation of the intestines.

I have already mentioned the condition as it is found after birth in cases in which the second stage of rotation does not occur. This condition is called "nonrotation of the intestine." This term disregards the first stage of rotation and considers only the second stage. In case of "nonrotation" the duodenum emerges on the right of the stomach, the small intestine occupies the right side, the colon the left side of the abdominal cavity. The small intestine and the proximal part of the colon are suspended from the same mesentery.

There also occur, even more rarely, other anomalies of intestinal rotation, one is the so-called "reversed rotation" in which the pre-arterial segment of the midgut rotates in clockwise instead of counter-clockwise direction around the colon, crossing it anteriorly instead of posteriorly. A third type of anomaly is called "malrotation," which comprises other more irregular abnormalities of rotation. The three groups of anomalies of the second stage of rotation have the one factor in common, that the small intestine and the proximal part of the colon remain suspended from one common mesentery. The designation "common mesentery" covers, therefore, all three conditions.

The most plausible theory concerning the cause of faulty rotations is the one of Dott<sup>3</sup>. That these anomalies are likely to occur in cases in which the opening of the physiologic umbilical hernia, through which the midgut has to return into the abdomen, is either wider or narrower than normal. If the opening is wider, it does not offer any obstacle to the simultaneous return of pre- and postarterial segments of the midgut and the condition of nonrotation is likely to follow. If the orifice is unduly narrow or of irregular shape, it interferes with the normal mechanism of return, and abnormal rotation of the two loop segments, "malrotation," may be the con-

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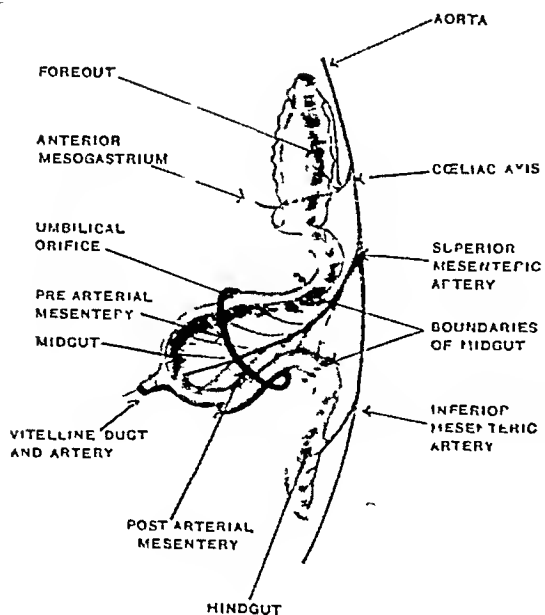


FIG 1—Primitive alimentary tract at about the fifth week seen from the lateral aspect

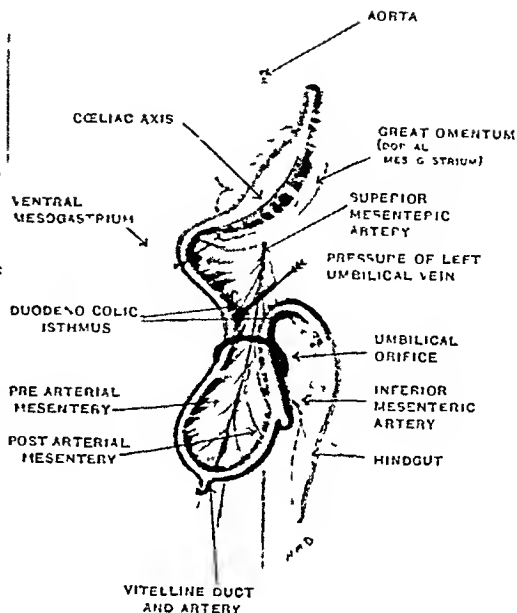


FIG 2—Condition of the alimentary tract at about the eighth week viewed from the ventral aspect First stage of rotation is completed

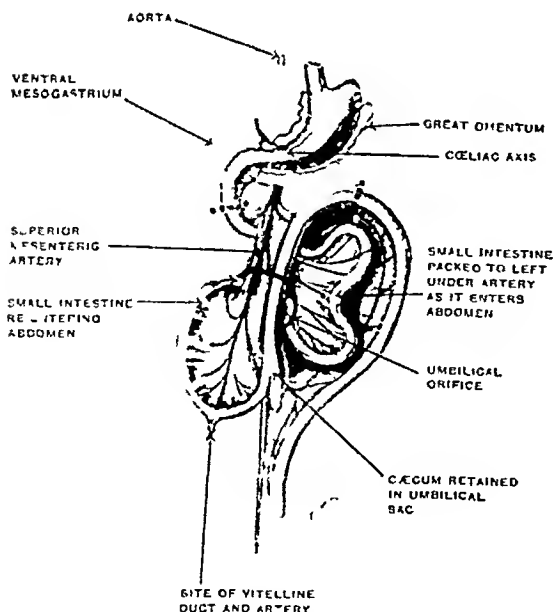


FIG 3—Condition found at the tenth week Return and contra clockwise rotation of small intestine beneath the superior mesenteric artery This constitutes the second stage of rotation

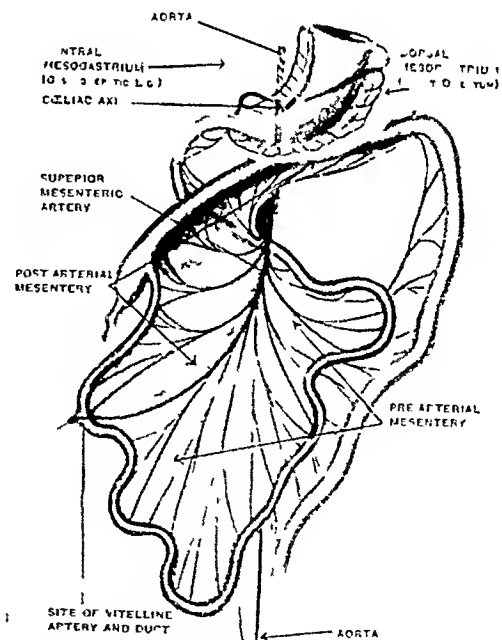


FIG 4—Normal condition of the alimentary tract at eleventh week Second stage of rotation completed

sequence Or an unyielding obstruction may even lead to postnatal persistence of the primitive umbilical hernia

Conditions of left-sided cecum produced by nonrotation and faulty rotation should not be confounded with the condition of "*situs inversus*," or complete transposition, which represents simply a mirror picture of the normal state The latter condition has been described relatively often, up to 1911, about 300 cases of "*situs inversus*" having been reported in the literature

However, a review of the literature, up to 1937, discloses that only about 120 proven cases of nonrotation and faulty rotation of the intestine have been described, though there is no question but that quite a few more have been observed but not reported

*Clinical Picture*—It is a well-known fact that anatomic deviations and malformations resulting from anomalies of the embryonic development leave the organs involved biologically and functionally weaker, and consequently predisposed to disturbances In nonrotation and faulty rotation we find lack of efficient fixation of the intestines, unduly narrow base and undue length of the common mesentery, which predispose to ptosis, torsion and volvulus Still, it is believed that the majority of people with anomalous rotation of the intestines may go through life without ever becoming aware of it through any disturbing manifestations Occasionally this condition is discovered accidentally when a patient is operated upon for appendicitis, or when a gastro-enterostomy is attempted Or it is found during an autopsy as incidental finding

Other individuals with the same anomaly present vague gastro-intestinal disturbances of varying degree, over shorter or longer periods of time They may be diagnosed and treated as cases of "chronic appendicitis," or "chronic cholecystitis" Some patients complain of occasional sudden attacks of abdominal cramps, not well localized, which may be accompanied by nausea and vomiting There may be periods of complete well-being between attacks

It is easy to understand that the diagnosis of nonrotation and faulty rotation cannot be made by the indefinite clinical symptoms, and can only be revealed roentgenologically

Complete intestinal obstruction may occur at any time and at any age in so predisposed individuals In cases with "reversed" and "malrotation," symptoms are likely to appear in earlier life They consist usually in torsion of the greater part or all of the midgut In patients with "nonrotation," symptoms are more likely to appear later and involve in the majority of cases only the ilocolic flexure Still, high duodenal obstruction was occasionally observed in the new-born during the first days of life as the result of nonrotation, while one case of volvulus from the same cause was reported in a man, age 76 Of 48 cases with common mesentery collected by Dott, in 1923, acute intestinal obstruction was observed in 13 Gardner and Hart<sup>4</sup> collected, up to 1934, 23 cases of volvulus in patients with this anomaly

# NONROTATION OF THE INTESTINE

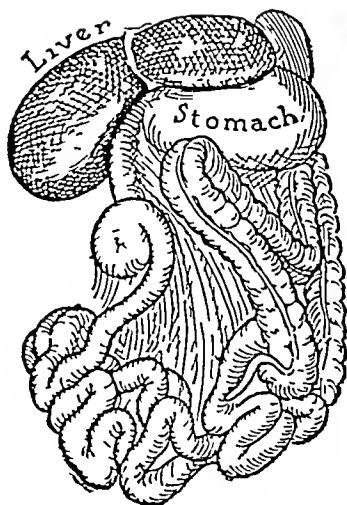


FIG 5—Postnatal condition in case of nonrotation of the intestine. Duodenum and small intestine found on the right side, colon on the left side of the abdomen.



FIG 6—Case 2. Roentgenogram showing the typical localization of the nonrotated small intestines, the duodenojejunal flexure and the jejunum occupying the right upper quadrant.



FIG 7—Case 2. Six hour roentgenogram before operation, showing the transverse colon hanging vertically down, ascending colon and cecum occupying the true pelvis.

FIG 8—Case 2. Postoperative roentgenogram after a barium enema. Cecum and ascending colon are fixed to the posterior peritoneum above the right iliac crest.

*Treatment*—No treatment is necessary for patients in whom the condition of anomalous rotation is found accidentally, or in whom only vague symptoms are present. For symptoms of torsion and volvulus, all authors recommend some form of fixation of the cecum and ascending colon.

#### CASE REPORTS

**Case 1**—Male, age 16, was admitted to hospital in July, 1937. Family history and early personal history irrelevant. Complained of recurrent attacks of abdominal pain over a period of three years, apparently brought on and aggravated by exertion, such as walking and standing for any length of time. Relieved upon sitting. Pain sharp and cramp-like, localized in right lower quadrant. Frequent eructation but no nausea or vomiting with earlier attacks. Spells more frequent and severe lately. Last attack, accompanied by vomiting, started several days prior to hospitalization.

*Physical Examination*—A well developed, well nourished boy, not acutely ill. Temp, 99.8° F, pulse, 104, resp, 24, general examination, essentially negative. No visible deformities. Abdomen. No distention, no cough impulse in either inguinal canal. Slight tenderness in right lower quadrant. Tentative and admitting diagnosis. Possible chronic appendix. Roentgenologic examination revealed a typical picture of nonrotation of the intestines.

*Subsequent Course*—Patient kept in bed under observation, temperature and pulse gradually went down, becoming normal after three days. No acute symptoms developed during hospitalization. Felt completely well after one week. His symptoms were not considered severe enough to justify operation. Patient was discharged with recommendation to remain under observation.

**Case 2**—Female, age 27, was admitted to the hospital in October, 1937, complaining of having suffered from repeated attacks of severe abdominal cramps for five months, which were accompanied by distention and nausea. They occurred apparently independent of food intake and exercise and were vaguely described as radiating from the right to the left side across the lower abdomen. The episodes lasted from one to several hours, requiring narcotics on several occasions before they subsided. Menstrual history was negative. There were no urinary symptoms.

*Physical Examination* showed a normally developed, fairly well nourished woman, not acutely ill. Temp, 98.4° F, pulse, 80, resp, 18. Genito-urinary and other systems essentially negative. Abdomen showed some distention in lower part. There was a slight tenderness of the entire abdomen, most marked to the right of the umbilicus, no rigidity. Roentgenologic examination revealed the typical picture of nonrotation (Figs 6 and 7).

*Operation*—Celiotomy corroborated the roentgenologic findings. The transverse colon was found hanging down in a vertical direction, the part of the colon corresponding to the hepatic flexure and the cecum were found in the true pelvis, appendix was pointing to the left, the ileocolic flexure was suspended from a long, narrow mesentrium, and was extremely mobile. Cecum and ascending colon were partially twisted, markedly distended, deeply congested and covered with an inflammatory exudate.

The cecum was brought up and turned, the appendix removed, the mesentrium of the cecum was taken up with several sutures, approximating it to the posterior peritoneum above the right iliac fossa.

Recovery was uneventful. Patient has been free of pain since operation. Post-operative roentgenologic studies showed a good anatomic result (Fig 8).

*Comment*—One interesting fact is often observed in cases of faulty rotation, namely, the discrepancy between the subjective symptoms and the findings of routine physical examination on the one side, and the actual condition as revealed roentgenologically and operatively on the other. In

other words, there is an incongruity between the descriptions of pain and tenderness in the right lower quadrant (indicated in both our cases and in similar ones cited in the literature), and the anatomic condition revealed—the right lower quadrant being free of any possible offending organ.

Charles Mayo<sup>5</sup> described two cases in which the unsuspected condition of nonrotation was complicated by inflammation of a left-sided appendix. In both patients the diagnosis of appendicitis was correctly made, but the suspected appendix was searched for in vain through a right McBurney incision. A second incision was necessary to reveal the existing displacement and to complete the operation.

Several factors may contribute to such errors in localization of abdominal pain in cases of faulty rotation. To some degree responsible may be the common medical habit and involuntary tendency to look for and to suggest localization of vague abdominal symptoms in the right lower quadrant.

Clinical experience has shown how difficult it is for the patient to localize and the doctor to interpret the source of any abdominal disturbance as long as it does not involve the parietal peritoneum. In cases of anomalous intestinal rotation one has to consider the additional fact that the change of position of the midgut does not essentially alter the path of the corresponding visceral nerves. The nerve stimuli from the proximal colon travel through the mesentery along the superior mesenteric plexus to the same ganglia, and along the same communicating branches up to the central nervous system, as in the normal individual. The potential faculty of the individual to localize visceral nerve impulses to certain corresponding areas must be essentially acquired and inherited through phylogenesis. Isolated deviations from the normal anatomic pattern of the species, as in faulty rotations of the intestines, do not imply a corresponding change of the inherited pattern of localization of visceral nerve impulses.

#### SUMMARY AND CONCLUSIONS

A short outline of the normal development of the primitive alimentary canal has been given in order to make the anomalies of the normal rotation understandable.

Most important is the so-called second stage of rotation, the most common of its typical anomalies is nonrotation.

Anomalies of rotation occur possibly more often than is apparent. The majority of such cases may not show any noticeable symptoms and are probably never discovered. Of the 120 cases described in the literature, less than one-half showed definite symptoms of torsion and volvulus.

The diagnosis of anomalous rotation can only be made with certainty roentgenologically or by celiotomy.

No treatment is necessary for this condition when accidentally discovered or when it produces only mild symptoms. For manifestation of torsion and early volvulus, some type of fixation is recommended.

Two cases are reported. The first patient, who presented only indefinite



and transient symptoms, was not thought ill enough to require surgery. The second one was operated upon for symptoms of torsion. Fixation of the proximal colon afforded complete relief.

Comment has been made on the difficulty, in general, of localizing intestinal pain by physical examination alone. This difficulty is increased in cases of abnormal rotation.

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# INTRA-ABDOMINAL OMENTAL TORSION

## REPORT OF THREE CASES

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OMENTAL torsion is a pathologic condition that has long been recognized and frequently described. In 1851, Marchette reported a case, and Oberst<sup>41a</sup> one in 1882. Later on a distinction was made between cases with a hernia combined with a torsion within or outside of the hernial sac and those without any definite hernia. Most of the cases occurred in the former group, the strictly abdominal or idiopathic omental torsion being a rarity. Corner and Pinches<sup>9a</sup> (1905) found among 41 cases reported only four without a hernia. There have probably been more than 200 cases reported up to the present time, but of these, scarcely more than 40 were of the strictly abdominal type. The latter can, therefore, hardly be considered worth the publication of a single case, but as only a very few cases have been published previously, as having occurred in Sweden, the following observations and appended case reports were thought to be of interest.

*Classification*—Omental torsions have been classified into different groups by many authors (Aimes,<sup>1</sup> Pretzsch,<sup>45</sup> Skeel,<sup>56</sup> *et al*), but the classification of Payr<sup>42</sup> (1906) is probably the most satisfactory, and is herewith appended.

### I Without a Hernia (entirely intra-abdominal)

- (a) Simple omental torsion, only the omentum itself being rotated
- (b) Complicated torsion, the omentum having adhered to some other abdominal organ together with which the rotation takes place

### II With a Hernia

- (a) Intra-abdominal torsion, without symptoms from the hernia
- (b) Intra-abdominal torsion, with previous inflammation or symptoms of kinking which have resolved spontaneously. The torsion is in this case entirely intra-abdominal
- (c) Entirely hernial (saccular) torsion, only the portions of the omentum inside the hernial sac being rotated
- (d) Combinations of the above

Usually only a minor part of the great omentum is twisted, but cases have been described of total omental torsion. The fact that the twisted part of the omentum is nearly always found in the right part of the abdomen has been ascribed to anatomic conditions. Some authors direct attention

to the frequency of appendicitis in the anamnesis of patients with omental torsion, a previous irritation of the peritoneum in such cases possibly having a localizing importance. Most of the hernial cases were right-sided inguinal herniae, seldom femoral.

*Incidence and Age*—A critical survey of the cases published up to the present time shows that the occurrence of omental torsions is greater in men than in women. The condition can occur at any age, the youngest case was three years of age, the oldest 79. However, by far the greatest part of the cases are between 30 and 50 years of age.

*Concomitant Pathology*—The presence of a hernia together with an omental torsion facilitates our comprehension of the factors governing the formation of the omental tumor, which must be considered the postulate for the creation of a torsion. Through atrophy and conversion into connective tissue the portion of the omentum strangulated in the hernial sac becomes firmer, the weight of this tumor favoring the formation of a stalk. Through torsion of the latter a typical condition of acute omental torsion is caused, with disturbances in nutrition and circulation. The omentum frequently becomes attached to the hernial sac by adhesions, and sometimes rotates around two axes.

*Etiologic Factors*—The etiologic factors in the cases of free omental torsions, without the presence of a hernia, are not clear, however, and several theories have been offered, some based upon experimental investigations, the best known of which are those of Payr<sup>42</sup> and Sellheim<sup>52a</sup>.

Payr ascribes the formation of an intra-abdominal torsion to hemodynamic forces. In the stalk of the omental tumor, following an inflammation or from some other cause, a change in its relative position may cause kinking. The stasis resulting in the tortuous veins favors the completion of the torsion, and finally occlusion of the straight arterial blood vessels occurs. The different specific gravity in the several parts of the omental tumor is said to predispose to the formation of torsions.

Sellheim<sup>52a</sup> is of the opinion that rotatory movements of the whole body are transmitted to the visceral organs. At the cessation of the rotatory movement of the body, the visceral organs continue that movement in different degrees. The same author puts great etiologic importance on the fluctuations in intra-abdominal pressure and intestinal peristalsis. In the several cases omental torsions were observed following violent movements of the body, such as occur in sports and gymnastics, a fact supporting the correctness of his theory.

Jungling<sup>27a</sup> calls attention to the possibility of a primary, congenital omental stalk. Other authors are of the opinion that thrombotic and embolic processes in the vessels of the omentum should be considered as etiologic factors. The importance of an antecedent appendicitis has been mentioned before (Melchior, Boss). Betz<sup>3</sup> points out the protective faculties of the omentum during infections in the abdominal cavity and its

self-sacrificing activity in this connection Poizelt<sup>44</sup> stresses the etiologic importance of a weakness in the walls of the blood vessels themselves

A clear and satisfactory explanation therefore, of the etiologic mechanism of these torsions has not yet been rendered, possibly the truth may lie in a combination of all of the theories offered Probably, however different etiologic factors dominate in different cases

*Symptomatology*—The symptomatology of the omental torsions in the beginning evidences, not infrequently, a shorter or longer period of diffuse abdominal complaints (indisposition, pains, obstipation, *etc*) An acute torsion is followed by rather severe pain in the right iliac fossa, sometimes however, spread more diffusely Vomiting and nausea are reported in most cases Inhibited passing of flatus is not uncommon Temperature and pulse are usually only moderately increased The leukocytes are reported to be low, but in most of the published cases they were definitely increased, in consideration of which a definite opinion cannot be stated Blood counts sometimes showed a displacement to the left The fact that the clinical aspect is very similar to an acute appendicitis is apparent on consideration that nearly all known cases have been operated upon under this tentative diagnosis Corresponding to the tenderness in the right iliac fossa one often finds some muscular resistance, and in many cases a resistant mass more medially located than is usual in perityphlitis The localization of the omental torsion can sometimes give rise to a suspicion of cholecystitis or a twisted ovarian cyst Riedel<sup>46</sup> reports a case with a resistant mass in the left iliac fossa, as in one of the cases described below

As has been said before, nearly all cases are diagnosed at operation In addition to appendicitis one must consider intussusception, intestinal tumors and ileocecal tuberculosis In cases of acute abdominal conditions with unusual symptoms, one should also bear omental torsion in mind

*Operative Findings and Prognosis*—At the operation one usually finds, after opening the peritoneum, quite a large quantity of serosanguineous fluid in the abdomen The twisted omental mass is usually loosely adherent to the adjacent organs or to the peritoneal wall As stated before, the size varies greatly On account of circulatory disturbances and infarction, it is purple and firm The stalk is sometimes twisted as many as five or more times Treatment consists in total removal of the twisted omentum The prognosis is good, the death rate in cases treated in time being less than 5 per cent The few cases of death reported have been in elderly patients with a complicating pneumonia

Three cases of intra-abdominal omental torsion are herewith reported, two of which have been placed at my disposal by my present chief and operated upon by him at the Gallivare Hospital

#### CASE REPORTS

**Case 1**—Hosp No 255/1925 Male, age 36, was admitted to the hospital complaining of pain on the right side of the abdomen, not severe enough to keep the patient from work, which had begun two days previously No vomiting or nausea No chills

On the day of admission the pain had become more severe, but no other complaints  
Micturition normal

*Physical Examination*—General condition good Heavily built, fat Heart dull, systolic murmur, no dilatation Lungs Occasional rales, diffusely spread Abdomen Tenderness and marked muscular resistance in the region of the appendix Indirect tenderness to the left, diminishing upwards toward the costal arch No palpable resistant mass Temperature  $38.3^{\circ}\text{C}$  Albuminuria

*Operation* (Dr Moller) Celiotomy plus Resection of Omentum Tentative diagnosis of appendicitis, with reservation for the nontypical course of the disease Under general anesthesia a diffuse, resistant mass was felt under the right rectus muscle extending high up but not quite to the costal arch On opening the peritoneal cavity liquid blood was found present No inflammatory exudate, or any other inflammatory phenomena were found on the intestines Cecum and appendix were not examined A second incision was made in the median line, above the navel, with the thought of finding a pancreatitis A firm swollen lobe of the omentum was felt above No free fluid was found in the upper part of the abdomen, or any fat necroses or injection of the viscera Downwards, to the right, a large firm mass was felt and easily delivered It consisted of a part of the great omentum, the size of a fist, firm, hemorrhagically infarcted, and twisted several times about its thin stalk A couple of tourniquets were applied to the stalk which was then ligated Suture Convalescence without complications

**Case 2**—Hosp No 1407/25 A male, age 12, had been treated at a sanatorium for pulmonary tuberculosis for ten months, and had been discharged three months previously He had become suddenly ill the day before admission to the hospital with pain in the lower abdomen Normal stools Increasing pain with vomiting and chills

*Physical Examination*—General condition moderately affected Temperature  $38.2^{\circ}\text{C}$  Abdomen not distended Tenderness over the entire abdomen but without signs of peritonitis Tenderness most pronounced in the left iliac fossa with marked resistance even on light palpation No resistant mass could be felt Urine normal

*Operation* (Dr Moller) Celiotomy plus Resection of Omentum Incision in the median line below and a little above the navel disclosed bloody fluid in the abdomen On the visible loops of the intestines typical tuberculous nodules were found No distention of the intestines The resistant mass, which was palpable in the left iliac fossa after general anesthesia had been established, was identified as a lump of the omentum, the size of a goose egg and loosely adherent to the left side of the entrance to the pelvis It was easily mobilized and was connected with the omentum by a thick stalk the size of a pencil and twisted so many times that it had nearly become severed The omental tumor was hemorrhagically infarcted and on its surface small, yellow tuberculous nodules were observed Catgut ligatures were placed around the stalk and the mass removed The abdominal effusion was sponged out Suture On cutting through the omental tumor an irregular, folded, caseous region was found in the middle of the hemorrhagically infarcted tissue Convalescence without complications

**Case 3**—Hosp No 1253/37, Borås Hospital A female, age 40, had complained for the past year, several times a month, of slight transient pain in the right iliac fossa No vomiting or nausea had occurred in connection with the attacks The day before admission she had become ill with similar pains in the right iliac fossa Went to work but had to discontinue because of the increasing pain She was nauseated and vomited several times No chills Stools normal Micturition normal Slept only a short time on the night before admission on account of the pain On the day of admission the pain had lessened but the abdomen had become more tender, both to pressure and movements

*Physical Examination*—General condition good, fat Weight 92 Kg Temperature  $38.3^{\circ}\text{C}$ , pulse 100 Heart and lungs normal Abdomen Soft, thick subcutaneous layer of fat Tenderness to the right, medially Indirect tenderness elicited No certain resistant mass The tenderness seems to be superficial No inguinal herniae Gyneco-

logic examination normal Rectum negative Urine normal On the diagnosis of appendicitis the patient was operated upon by the author

*Operation*—Celiotomy Plus Appendicectomy, and Partial Resection of the Omentum Slightly increased amount of fluid in the abdomen The appendix was found but looked innocent Removed as usual Intestines slightly injected, but not distended No Meckel's diverticulum Uterus and right adnexa normal Gallbladder could not be reached through the incision On palpation upwards, toward the navel, an omental tumor was felt just to the right of the median line approximately at the site of maximum tenderness The tumor was delivered into the wound It consisted of a twisted part of the omentum about 8 cm long and 3 cm thick, tapering toward the poles It was light purple and rather firm in consistency On both poles were stalks connecting the tumor with the rest of the omentum Both these stalks were twisted three to four times The pathologic portion of the omentum was removed Suture Microscopic examination of the resected portion showed a recent hemorrhagic infarct without any positive older characteristics (Forselius) Convalescence without complications

The three cases of omental torsion reported herewith seem to have occurred entirely intra-abdominally, without concurrent herniae In the first and third cases, no positive or plausible etiologic factors could be found, but the second case had a tuberculous process in the peritoneum and omentum, which, with some certainty, had predisposed the omentum to the torsion, especially as the twisted part contained a firmer caseous portion The diagnosis before operation was appendicitis in all the cases

#### SUMMARY

The author has surveyed the literature on omental torsions and the theories of their genesis The clinical aspect is practically impossible to separate from that of appendicitis Three cases of entirely intra-abdominal torsion are detailed In only one of these was a plausible etiologic factor found

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# SPLENECTOMY IN VARIOUS BLOOD DISORDERS

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SPLENECTOMY has come to be a well recognized part of the therapy of certain disorders of the blood and blood forming organs, notably in congenital hemolytic jaundice, thrombopenic purpura and Banti's disease, although we must admit that both the rôle played by the spleen in the production of these disease pictures and the exact factors which bring about improvement after its removal are not clear. This will continue to be true until means are found to reproduce these disease pictures in animals, and the efforts that are being made in this direction with results that are just now beginning to be reported give definite hope that the elucidation of some of these questions is not too far off. Fortunately, it is true of splenectomy in these three conditions that the results amply justify its use, but attempts to expand the indications much beyond these have been attended, almost uniformly, by a considerably higher mortality and by disappointing results so far as cures are concerned.

Such experiences are difficult to avoid, however, as the boundaries of our diagnostic categories cannot be entirely fixed and some borderline cases, or others in which the diagnosis is not entirely clear, are to be found in any series. We are reporting herewith a series of 50 patients who have been subjected to splenectomy at the New York Hospital during the past five years. Table I shows the diagnoses, predicated upon the clinical and laboratory data, the course or postmortem findings, in these cases.

*Operative Technique*—In all cases a long left rectus incision was made, extended as high as possible into the substernal notch. The lower pole of the spleen was freed of any adhesions to the omentum or transverse colon and delivered into the wound after which the peritoneum was incised just lateral to its reflection from the spleen, and the incision continued upwards to the upper pole of the viscus. The spleen was then delivered as completely as possible into the wound and the individual vessels doubly ligated with silk and divided, beginning at the lower pole and dealing with the vasa brevia last. In many cases, and particularly in the large spleens occurring in instances of hemolytic icterus, the injection of 1 cc. of adrenalin just before delivering the organ is of great aid in bringing about a considerable contraction, thereby facilitating its delivery into the wound. This also expresses blood from the spleen into the circulation to the amount of 500 cc. as indicated by Miller and

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Rhoads<sup>1</sup> In all cases the wound was closed completely with silk sutures and in a few instances silver wire stay sutures were employed

CONGENITAL HEMOLYTIC JAUNDICE—Representing the purest type of chronic hemolytic anemia due to intrinsic factors, this condition is characterized by increased fragility of the red cells in hypotonic salt solution and by spherocytosis, reticulocytosis, splenic enlargement, and a positive indirect van den Beigh reaction There is no notable racial or geographic distribution, or sex incidence

TABLE I  
DIAGNOSES IN 50 CASES SUBJECTED TO SPLENECTOMY

Diagnosis	No of Cases	Operative Deaths
Hemolytic jaundice	17	0
Thrombocytopenic purpura	12	0
Atypical purpura hemorrhagica	2	0
Banti's syndrome	8	0
Cooley's anemia	4	0
Refractory primary anemia	3	1
Nodular cirrhosis	1	1
Retothelial sarcomatosis	1	1
Nonlipoid histiocytosis	1	0
Leukemia	1	0
	50	3 (6%)

The underlying anomaly responsible for the fragility of the cells is apparently congenital and hereditary, being transmitted as a mendelian dominant by either parent<sup>2</sup> Other members of the patient's family may also be shown to have this anomaly, and in them the disease may be said to exist in a latent form Some authors have postulated the existence in some cases of a "trigger mechanism" which may convert the latent into the acute form of the disease, and base their theory on the simultaneous onset of hemolytic crises in several members of the same family at the same time In many patients the onset of acute symptoms of hemolysis dates from a respiratory infection or other minor ailment

Gansslen<sup>3</sup> first connected the fragility of the red cells with their increased sphericity, and others have repeatedly demonstrated this characteristic Haden<sup>4</sup> has pointed out that a red cell which has lost its biconcave configuration and has assumed a more nearly spherical shape can take up less fluid without rupture, and explains the increased fragility of the erythrocytes on this basis It should be emphasized, however, that in some patients with this disease no increased fragility of the red cells in hypotonic saline is demonstrable, and that in those in which it is found to exist the degree of hemolysis *in vitro* bears no direct relation to that in the patient's circulating blood nor to the severity of the anemia

Symptoms—The severity of the symptoms varies greatly in different patients and also in the same patient from time to time, as the hemolysis tends

to occur in crises. The chief complaints may be weakness, fatigue, and dyspnea due to anemia, or merely vague abdominal discomfort due to the splenic enlargement. The hemolytic crises are often ushered in by attacks of nausea and vomiting, associated with some fever. Since gallstones are found in about two-thirds of the chronic cases, the initial symptoms are occasionally referable to the biliary tract. Chronic pigmented leg ulcers are present in some cases.

*Physical Signs*—The typical clinical signs of hemolytic jaundice are anemia, splenomegaly and jaundice. The skin presents the typical lemon-yellow color and the urine fails to give a positive reaction for bilirubin, although urobilin may be present. The spleen is sufficiently enlarged to be palpable in 85 per cent of the cases, and in some may reach enormous proportions. It may vary in size from time to time, tending to increase during the hemolytic crises, as the enlargement would seem to be due to overactivity in its rôle as the chief site of destruction of the red cells and consequent overloading with cells in the process of disintegration.

*Blood Findings*—The degree of anemia varies considerably according to the acuteness of the disease, but may reach a severe grade during the hemolytic crises. The red blood cell counts before splenectomy ranged from 1,200,000 to 4,500,000, in the cases in this series, the average of the 17 being 2,800,000, while the hemoglobin values were from 25 to 93 per cent, with an average of 57 per cent. These figures are in agreement with the frequently emphasized fact that the color index is higher in hemolytic icterus than in any other type of severe anemia except pernicious anemia, being commonly in the neighborhood of 1.

The reticulocyte count is characteristically raised, and in our series varied from normal to 48 per cent. Fourteen of the cases had more than 5 per cent reticulocytes in the circulating blood, and in 10 the value was 35 per cent or higher. There is often a fairly close correlation between the reticulocyte count and the severity of the anemia, a point of definitely good prognosis, indicating as it does a considerable capacity on the part of the bone marrow to restore the red blood cell count to normal once the spleen, as the chief destroyer of these elements, is removed. This excessive bone marrow activity, particularly in children, may bring about changes in the bones demonstrable by roentgenologic examination suggesting those seen in leukemia, and certain authors<sup>5</sup> comment on changes in the bones of the skull not unlike those seen in the erythroblastic anemia of Cooley. Neither of these changes was a feature of any of our cases.

The characteristic erythrocytes in this condition are dense cells of decreased diameter, although there may be considerable variation in size throughout the smear. The microcytosis is only apparent, however, as Naegeli<sup>6</sup> and others<sup>7</sup> have shown that the cell volume is normal or actually increased.

Finally, rare cases of this condition are encountered in which there is a generalized lymphadenopathy in addition to splenomegaly, or more rarely appearing after splenectomy, perhaps due to the activity of the reticulum cells.

of the nodes in destroying red cells—such a finding is of poor prognostic significance

**SPLENECTOMY IN HEMOLYTIC JAUNDICE**—In the light of our present knowledge of the rôle of the spleen in the destruction of red cells, its removal would seem definitely indicated in this condition in which the cells are abnormally fragile. It should be remembered, however, that the destruction of red blood cells is a function of the reticulo-endothelial system in which the spleen plays a dominant rôle because of the concentration of a large portion of the elements of this system in that organ. By removing the spleen, therefore, we remove only a portion of the cells responsible, but fortunately, a sufficient portion to restore a more nearly normal balance between blood formation and blood destruction in most cases.

In a typical case the indications for splenectomy are obvious and overwhelming, and the question resolves itself into one of selecting the optimum time for operation. As a rule, it may be said that we should avoid operation when the patient is going into a hemolytic crisis, and perform splenectomy as the crisis is receding or in a free interval. This is not always possible, however, as the crises may be very severe or recur so frequently as to leave little choice. In general, the patients stand the operation well as the spleen, though often much enlarged, is seldom adherent and can usually be removed quite easily.

It is in this type of case that the use of adrenalin (1 cc subcutaneously) is most important at the moment of delivery of the spleen and before ligation of the pedicle, as it produces a definite contraction of the rather soft viscus and squeezes out a considerable quantity of blood into the circulation, tantamount in some instances to an infusion of 500 cc of the patient's own blood.

More debatable is the question of splenectomy in patients who have the disease in a latent form, many of whom undoubtedly may go on for years or even throughout life without developing acute symptoms. Such patients should be kept under close observation, and operation advised if any tendency to abnormal hemolysis is noted, as even a very long period of freedom from symptoms is no guarantee of their continued absence. One of our patients developed acute symptoms at age 58, including an anemia of 1,600,000 red cells, but fortunately with a very high reticulocyte count. She stood operation well and has made an uneventful recovery.

The results in the cases of familial hemolytic jaundice in series, together with the preoperative and latest postoperative blood studies, are shown in Table II.

There were no operative deaths, but two patients have died since operation. One of these, a woman, age 44, died of pneumonia four years after operation. She was also suffering from gout at the time that her spleen was removed, and while definitely improved by operation, so far as her blood picture was concerned, her count rarely reached 4,000,000 and was usually about 3,300,000.

TABLE II  
PRE- AND POSTOPERATIVE BLOOD STUDIES AND RESULTS IN 17 PATIENTS SUBJECTED TO SPLENECTOMY FOR HEMOLYTIC JAUNDICE

Case	Sex	Age	Major Complaint	Hemoglobin		RBC Count		RBC Fragility		Reticulo-cyte Percentage	Follow-up	
				Preoper	Latest	Preoper	Latest	Begins	Ends		Duration	Result
W C	M	15	Weakness	50	103	2.9	4.2	6	—	10	4½ yrs	Good
A C	F	44	Anemia	56	49	2.7	2.3	55	—	11	4 yrs	Died
F R	M	22	Jaundice	79	124	4.0	5.0	65	—	2	5 yrs	Good
J J	M	25	Jaundice	93	126	4.4	6.0	5	—	19	5 yrs	Good
J C	F	7	Jaundice	28	71	1.2	3.4	8	—	14	2 yrs	Fair
M S	F	17	Jaundice	88	100	3.8	4.1	5	—	11	1 yr	Good
R S	F	29	Anemia	62	105	2.6	4.3	5	—	13	1 yr	Good
P H	M	5½	Anemia	54	70	3.5	3.8	4	—	8	1 yr	Good
M M	F	23	Jaundice	89	113	4.5	4.8	6	—	8	1½ yrs	Good
W S	M	12	Anemia	25	53	2.6	2.2	5	—	30	3 mos	Died
J N	M	15	Jaundice	70	129	2.4	5.4	58	—	5	4 yrs	Good
E H	F	60	Anemia	41	124	1.8	4.6	55	—	33	3½ yrs	Good
G M	M	31	Jaundice	38	76	1.6	4.0	6	—	1	3 yrs	Good
M R	F	31	Jaundice	33	113	1.7	4.4	6	—	40	2½ yrs	Good
S P	M	9	Anemia	65	115	3.5	5.2	5	—	20	2½ yrs	Good
A S	F	59	Anemia	52	91	1.6	3.8	6	—	48	1½ yrs	Good
E W	M	5	Anemia	55		2.5		5	—	20	11 mos	Good*

\* This patient left the country soon after operation, but writes that he is asymptomatic

The second patient, a boy, age 12, died three months after operation. A summary of his history is appended.

**Case Report**—W. S., male, age 12, began to have symptoms of anemia and jaundice about three and one-half months before operation. His past history was irrelevant and the family history was negative. Tests of the blood of his brothers and sisters showed no increased fragility of the red cells.

His present illness began with very easy fatigability, noticed particularly after playing, and with pallor noted by his parents. During the next two weeks he became progressively more anemic and more listless. He was admitted to another hospital where it was found that he had a red blood cell count of 1,150,000, hemoglobin, 28 per cent, white blood cell count of 750, reticulocytes, 31 per cent, clotting and bleeding time, normal, and fragility test of red blood cells, normal, icteric index, 30. He was given three blood transfusions with a slight improvement in his red count, and was transferred to the Hospital of the Rockefeller Institute five weeks later.

**Physical Examination and Laboratory Data**—In addition to the findings previously noted, it was then discovered that he had generalized lymphadenopathy and a considerably enlarged spleen. Red blood cell count 1,800,000, hemoglobin, 38 per cent, reticulocytes, 20 per cent, fragility tests again were normal. Bone marrow biopsy revealed extremely active erythroblastic marrow. Subsequent fragility tests showed slightly increased susceptibility of the red cells to hypotonic saline solution. On the basis of these findings of slightly increased fragility, persistently high reticulocyte count and an active erythroblastic marrow without bile in the urine, a diagnosis of hemolytic jaundice was made.

**Subsequent Course**—After several transfusions, he was transferred to the New York Hospital where splenectomy was performed March 8, 1934, and he was discharged April 4, 1934. Following operation he improved slightly. The red blood cell count was only slightly elevated, ranging around 2,000,000, but the hemoglobin was increased to 50 per cent. Reticulocytosis persisted. He gained weight, from 68 to 74 pounds. About two and one-half months after operation, however, he developed severe diarrhea accompanied by cramps, and vomited dark brown fluid without blood or coffee-ground material. The vomiting persisted, he developed constipation, and when admitted to the hospital, was complaining of severe pain in the upper right quadrant. He showed considerable anemia, and persistence of jaundice. The abdomen was distended and tense, the liver palpable and quite tender. Laboratory findings showed an icteric index of 26, blood chlorides, 500, urea nitrogen, 9, urine, 2 plus albumin and positive for bile and acetone. Bleeding and clotting time, normal. The vomitus contained bile. Fragility test, normal, red blood cells, 1,700,000, hemoglobin, 48 per cent, white blood cell count, 2,200, reticulocytes, 32 per cent.

Because of persistent pain in the upper right quadrant, exploratory celiotomy was performed but disclosed nothing other than a considerable quantity of clear bile-stained fluid in the peritoneum. Postoperative course was progressively downhill, and he died about 24 hours after operation.

**Autopsy** revealed thrombosis of the stump of the splenic, mesenteric and portal veins, hemorrhagic infarction of the jejunum and ileum, peritonitis, and generalized enlargement of the lymph nodes. **Microscopic Examination** of the spleen showed a normal capsule, with fewer and more widely separated trabeculae than usual. The splenic follicles show well-developed and active "germinal centers," but there is merely a thin rim of adult lymphocytes about these. The reticular tissue is moderately increased. The arterioles are contracted, but not collapsed, while the sinuses are well opened. Scattered about are numerous large mononuclear cells filled with a brown pigment. There are a few areas where these are grouped into tubercles, composed of large epithelioid cells, without any giant cells or caseation and containing a peculiar mesh formation that stains bright red with the Masson technic. These are not very numerous. A few eosinophils may be found here and there. **Diagnosis**—Splenomegaly of the indeterminate type seen in familial jaundice.

The liver showed extensive deposits of hemosiderin in the Kupffer's cells and liver cells and considerable phagocytic activity of the former. Erythrophagocytosis is occasionally seen in all the blood-forming organs. The bone marrow showed active erythropoiesis with many normoblasts and some megaloblasts.

The somewhat tenuous evidence of increased fragility of the red cells, together with the lack of such stigmata in the brothers and sisters, makes the diagnosis of familial hemolytic jaundice somewhat equivocal, and it may be that this case falls in the group of the acquired type. In this patient it would seem that to a lesser extent before and, to an even greater extent, after splenectomy the reticulum cells outside the spleen were actively engaged in the destruction of red blood corpuscles, thereby preventing the restoration of the balance between blood destruction and blood formation. The reason for the development of the portal thrombosis is not clear since the platelets after operation were never above 300,000 and for the most part ranged between 100,000 and 260,000.

**THROMBOCYTOPENIC PURPURA**—This disease, of which there were 12 cases in this series, is characterized by purpura and spontaneous hemorrhages and by a marked decrease in the number of platelets in the circulating blood. The bleeding time is prolonged and the clot shows poor retraction. Here, too, there is no peculiar racial or geographic distribution, but the disease is definitely more common in women. The condition appears in both acute and chronic forms, the latter being about nine times the more common. In most of the cases the onset is fairly abrupt, the initial symptoms being epistaxis, or bleeding from the gums or rectum, or copious and prolonged menstrual flow. Some patients report the apparently spontaneous appearance of purpuric spots on the skin or note that they bruise easily and develop extensive ecchymosis from relatively trivial trauma. In the acute form a severe grade of anemia ensues within a few months, but in the more chronic form the condition may exist for years without the development of anemia of more than slight or moderate grade. In five of our cases the symptoms had been present for less than eight months, while in six more they had been noted for from two to four years. One patient had had symptoms for 19 years before operation.

One must admit in the present state of our knowledge that the etiology of the condition is still obscure. Thrombopenia has been produced in numerous ways such as by the injection into an animal of an antiplatelet or antispleen serum developed in another animal,<sup>8, 9</sup> or by the injection of various toxic and irritating substances into the blood stream.<sup>10</sup> Tioland and Lee<sup>11</sup> have recently reported the thrombopenia-producing action of an acetone extract of spleens removed from patients with this disease, and find similar extracts of normal spleens inactive in this regard. However, mere thrombopenia does not seem capable of producing all the changes seen in this disease, and the weight of opinion agrees with the suggestion originally made by Hess<sup>12</sup> that changes in capillary permeability also play a rôle.<sup>8, 13, 14, 15, 16</sup> This has led to the suggestion that the disease really involves the entire reticulo-endothelial system.

Kaznelson<sup>17</sup> first suggested and Schloffer<sup>1</sup> employed splenectomy for the treatment of this condition, basing the suggestion on the idea that the spleen is the site of disintegration of the platelets. The cessation of hemorrhages was immediate and the platelets became markedly increased—a phenomenon now well recognized. To be sure, operations other than splenectomy also may cause an elevation of the platelets, but none to the striking degree seen after splenectomy both for this and other blood diseases. It would seem that we must assume that splenectomy cures the disease for one or both of two reasons, either it eliminates a major site of platelet destruction, or removes an organ which in this disease, at least, has an inhibitory effect on the formation of these blood elements, and perhaps exerts still other deleterious effects.

*Diagnosis*—As previously mentioned, the characteristic symptoms and signs of thrombopenic purpura are, as the name implies, thrombopenia and purpura, but to these may be added capillary fragility as evidenced by the tourniquet test, and in the blood studies, prolonged bleeding time, poor retractibility and increased fragility of the clot, and normal or slightly elevated leukocyte count. The spleen is but rarely palpable. In the very acute cases, the differentiation from aplastic or hypoplastic anemia or from aleukemic leukemia may be extraordinarily difficult, and yet the strikingly different results which follow splenectomy (in the former and latter conditions) render this necessary if in any way possible. The normal or even slightly elevated leukocyte count—particularly after hemorrhage—in true thrombopenic purpura is of aid in making the differentiation from aplastic anemia and the presence of relatively large numbers of young white cells in the circulation in leukemia may help in excluding it. Finally, the bone marrow biopsy is of great aid, but its reliability has been questioned since only a very minute area of the marrow can be examined by biopsy and even in true aplastic anemia isolated areas of hyperplastic marrow may be discovered.

*Treatment*—Splenectomy is now recognized as indicated and gives excellent results in the typical cases associated with definite thrombopenia. However, the very high mortality in the acute cases in the earlier reported series—as high as 87 per cent in some reports—compared with the apparent safety of the operation in the chronic type of the disease—led surgeons and internists alike to condemn splenectomy in the acute stage. This mortality has been steadily falling, however, and some of the most brilliant results have followed early operation. However, it must be said that patients with the disease in the acute form are not good operative risks and that very fact will deter surgeons from operating upon them except as all other measures fail.

Various medical measures, particularly repeated blood transfusions, may arrest the hemorrhage, or even bring about an enduring remission of the disease in some cases and the injection of ascorbic acid is sometimes capable of producing remarkable improvement or remission. However, in many cases, even these measures fail to stop the bleeding entirely or to restore the blood picture to normal, and but rarely produce the really spectacular results often seen following splenectomy.



TABLE III

PRE- AND POSTOPERATIVE BLOOD STUDIES AND RESULTS IN 12 PATIENTS SUBJECTED TO SPLENECTOMY FOR THROMBOCYTOPENIC PURPURA

Case	Sex	Age	Duration of Symptoms	Major Complaint	Hemoglobin		RBC Count		WBC Count		Platelets		Follow-up Duration	Result
					Preoper	Latest	Preoper	Latest	Preoper	Latest	Preoper	Latest		
A Y	F	25	4 mos	Hemorrhage	20	88	1 1	4 7	4 0	5 5	60	238	3 yrs	Good
N H	M	11	2½ mos	Hemorrhage	59	88	4 0	4 7	11 0	9 0	19	198	4½ yrs	Good
M C	F	14	16 mos	Hemorrhage	78	75	4 4	4 7	12 0	11 0	60	400	1 yr	Good
C H	F	32	4 yrs	Purpura	92	105	3 7	4 3	7 8	10 0	76	220	20 mos	Good
K B	F	52	4 yrs	Hemorrhage	63	96	2 9	4 4	5 2	7 4	50	290	1 yr	Good
M B	F	29	4 yrs	Purpura	92	92	4 9	4 0	9 8	6 3	60	230	6 mos	Good
M M	M	21	19 yrs	Hemorrhage	90	109	4 6	4 3	7 6	8 6	68	750	1 yr	Good
E M	M	7	2 yrs	Purpura	89	93	4 4	4 8	8 8	8 0	50	50 (po)	4½ yrs	Good
E F	M	19	5 mos	Hemorrhage	30	106	1 5	4 0	1 4	7 5	30	170	2½ yrs	Good
M G	F	3½	4 mos	Hemorrhage	74	52	3 5	2 4	7 4	5 2	6	10	5 mos	Died
G K	F	27	3 yrs	Hemorrhage	65	90	4 4	4 4	8 0	11 2	42	400	6 mos	Good
N S	F	34	3 yrs	Hemorrhage	80	99	4 0	4 2	4 0	5 0	50	270	1 yr	Good

TABLE IV

PRE- AND POSTOPERATIVE BLOOD STUDIES AND RESULTS IN TWO PATIENTS SUBJECTED TO SPLENECTOMY FOR ATYPICAL PURPURA HEMORRHAGICA

(Without Thrombopenia)

Case	Sex	Age	Duration of Symptoms	Major Complaint	Hemoglobin		RBC Count		WBC Count		Platelets		Follow-up Duration	Result
					Preoper	Latest	Preoper	Latest	Preoper	Latest	Preoper	Latest		
S G	M	14	8 mos	Hemorrhage	80	99	4 0	4 2	10	11	180	210	3 yrs	Good
M M	F	46	28 yrs	Purpura	105	94	4 4	4 3	6	9	288	440	1 yr	Poor

The present series comprises 12 cases of thrombopenic purpura, seven female and five male, whose ages ranged from three and one-half to 52 years. Five of the patients had severe anemia at the time of operation, and two were operated upon with red cell counts of 1,500,000 and 1,100,000 respectively. The spleen was considerably enlarged in one case due to the presence of a huge hemangioma. A summary of these cases appears in Table III.

There were no deaths from the operation in this group, although one patient died five months after operation with persistent thrombopenia and anemia. It is possible that we were mistaken in our diagnosis and that she should have been classified as a case of aplastic anemia. All the remainder are well and have practically normal red cell counts from six months to four and one-half years after operation. The platelet counts are known to be normal in all except one who has not been back to the Follow-Up Clinic. She writes, however, that she is free of her symptoms. One patient had a high platelet count at the time of the last observation.

Splenectomy was also performed in two cases of atypical purpura hemorrhagica, atypical in that they did not present thrombopenia. In one, a boy of 14, who had had symptoms of hemorrhage, purpura and the development of ecchymosis from slight trauma for eight months, an excellent result was obtained. The other patient was a woman of 39, who had had similar symptoms for many years. During the year which has elapsed since her operation she has shown no improvement (Table IV).

**BANTI'S DISEASE (SPLENIC ANEMIA)**—Although Gleisinger is said to have used the term "splenic anemia" in 1866, it was Banti, in 1883, who first gave impetus to the study of this condition, and Osler,<sup>18</sup> in 1900-1902, added to our knowledge of the clinical picture. Banti<sup>19</sup> described the disease as characterized by progressive splenomegaly, anemia of the microcytic type, leukopenia, slight thrombopenia and hematemesis, and progressing to obvious cirrhosis of the liver with jaundice and ascites. He also considered phlebitis of the portal vein as a uniform finding of the disease. From his description one infers that he considered that the primary seat of the disease was to be found in the spleen, and yet he shows some reservation by insisting that the process must be without obvious cause.

If one excludes the cases with obstruction to the splenic vein itself by tumor, thrombus, *etc.*, it is difficult to segregate into any single etiologic group the cases with the above clinical findings except that of portal cirrhosis. In the past, many other types of cases were included in this category but as the knowledge regarding them has increased, those which may be consigned to this group have steadily decreased in number. However, there is accumulating an increasing mass of direct and indirect evidence to indicate that the splenomegaly and attendant anemia are probably not due to primary disease of the spleen, but rather that the initiating factor involves the liver primarily and the spleen secondarily, which results in an overloading of the portal system with demonstrable elevation of pressure in the splenic vein.<sup>20</sup> The fairly constant splenomegaly seen in cases of portal cirrhosis, a splenomegaly the characteristics and effects of which are quite indistinguishable from that of

Banti's disease, attracts one to this view, and indeed, one is left with the feeling that the diagnosis of the latter syndrome rests on the dictum that in its early stages cirrhosis is not clinically demonstrable

This is a distinctly tenuous argument, however, as indicated by the repeated observation that microscopic cirrhosis, or definite periportal fibrosis, can exist without being clinically obvious or even detectable on gross examination of the liver. In the present small group of eight cases, four patients showed gross cirrhosis at operation, and in several, careful estimation of liver function by different tests indicated definite abnormality. Moreover, the literature contains several reported series of cases, operated upon under the diagnosis of Banti's disease, in which the liver was carefully observed or biopsies were made, and in which hepatic disease was so uniformly observed as to throw considerable doubt on the thesis that the splenomegaly was primary. Studies of cases of schistosomiasis, and lately the interesting work of Whipple and his associates at the Presbyterian Hospital in producing all the characteristic splenic, hepatic and hematologic changes by the injection of particulate matter into radicals of the portal system, present powerful arguments for considering overloading of the portal system the primary etiologic factor in the condition, the splenic changes being explicable on the basis of chronic passive congestion. In view of all this evidence, it would seem "an act of faith rather than of reason to believe in the primary nature of the splenic involvement" (Castle and Minot<sup>21</sup>)

One fact, however, remains as a deterrent, namely, that the results of splenectomy in recognized cirrhosis of the liver have not been such as to commend the procedure in most cases, whereas, the operation in patients with so-called Banti's disease has yielded many excellent results. It may be, however, that surgeons have been laggards in performing splenectomy in cirrhosis while they have had recourse to the procedure early in the course of Banti's disease. Recent reports tend to lend support to this idea.

The typical cases grouped in this category are young adults in whom the disease has been of insidious onset with weakness, digestive disturbances, easy fatigability or hematemesis as the presenting symptoms. The disease may begin in early life and commonly runs a chronic and protracted course. Pain over the enlarged spleen or over the liver, associated with inflammation of the capsules of these organs, may be encountered.

On physical examination, aside from those patients admitted in shock from acute hemorrhage, pallor and splenomegaly are the most prominent findings. The spleen is considerably enlarged and quite firm. In the later stages ascites may be present. Four of our patients were admitted after having had severe gastro-intestinal hemorrhage as evidenced by hematemesis or melena or both.

Examination of the blood in these cases shows a moderate anemia of the hypochromic type. In the present series the average red blood cell count was 3,360,000 before operation and the hemoglobin 64 per cent. Leukopenia is a quite consistent feature and may be marked, before operation in our own cases,

Case	Sex	Age	Symptoms	Major Complaint	Hemoglobin		R B C Count		W B C Count		Platelets		Follow-up
					Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	Pre-oper	Post-oper	
F W	M	32	1½ yrs	Pain, L U Q	78	96	Mil	Mil	Thous	Thous	Thous	Thous	Duration
E T	M	20	3 yrs	G I	32-88	101	4 0	1 8-	4 0	1 0	6 3	125	310
D S	F	25	3½ yrs	hemorrhage						4 6	7 7	100	1½ yrs
W M	M	29	1 yr	Weakness	70	90	4 9	3 2	4 3	3 1	7 0	310	6 mos
C G	M	37	6 mos	hemorrhage	40	111	2 5	4 2	4 3	3 6	24 0	200	9 mos
M F	F	38	3½ mos	Hematemesis	60	105	2 7	4 4	4 4	5 0	7 0	170	2½ yrs
A K	F	35	1 yr	Abd mass	86	90	4 4	4 3	4 3	3 0	13 0	350	2 yrs
V L	F	16	13 yrs	jaundice	65	94	3 8	3 7	3 7	6 6	12 0	190	3½ yrs
				G I	81	92	4 5	5 0	3 2	5 5	normal	740	1½ yrs
				hemorrhage									Good

TABLE VI												
PRE- AND POSTOPERATIVE BLOOD STUDIES AND RESULTS IN FOUR PATIENTS SUBJECTED TO SPLENECTOMY FOR ERYTHROBLASTIC ANEMIA (COOLLY'S)												
Case	Sex	Age	Major Complaint	Hemoglobin		R B C Count		W B C Count		Platelets		Follow-up Duration
				Preoper	Latest	Preoper Mil	Latest Mil	Preoper Thous	Latest Thous	Preoper Thous	Latest Thous	
A G	F	8	Anemia	61	50	2 6	3 3	10 0	10 0	360	4 yrs	Fair
F G	M	4	Anemia	55	38	2 6	1 7	10 0	10 0	400	8 mos	Died
L G	M	19 mos	Anemia	50	50	2 8	3 0	9 6	288	3½ yrs	Fair	
L S	M	5	Anemia	32	26	2 0	1 5	11 0	120	2 yrs	Died	

ranging from 1,000 to 6,600 (average, 3,650), after operation leukocytosis is the rule. Moderate thrombopenia is common before splenectomy, but after operation the platelets may reach high levels. Slightly increased resistance of the red cells to hypotonic saline is also a feature of the typical case.

*Splenectomy*—The removal of the spleen in this condition seems definitely warranted in the early stages and may alleviate some of the symptoms over a considerable period. The benefit which results would seem to be due to the reduction of the amount of blood coming to the liver through the portal vein which follows splenectomy. However, the operation is attended with certain risks since the spleen is commonly adherent and has developed a collateral circulation at its upper pole which may be difficult to handle. Further, as noted above, in many of the patients the platelets reach very high levels after operation and thromboses are not uncommon. Indeed, if one accepts the criterion of an unexplained febrile course as possibly indicating thromboses, this complication would seem to be quite common in this disease.

There were no operative deaths in this series of eight cases, but one patient (M. F.) died two years after operation of progressing cirrhosis with ascites. The longest time which has elapsed since operation is three and one-half years, and two additional patients have suffered recurrence of hemorrhage (Table V).

In general, the operative mortality is higher in this condition than in either of the foregoing and the results less satisfactory. Pemberton<sup>22</sup> reports 167 splenectomies for this condition with 16 deaths. The remaining 151 patients were followed for as long as 22 years, and 52 of them had died—more than one-third from recurrence of hemorrhage. Similar study of 118 operations for hemolytic jaundice showed four operative deaths and only seven additional fatalities occurring during the follow-up period.

**ERYTHROBLASTIC (COOLEY'S) ANEMIA**—The present series includes four cases of this peculiar type of anemia of childhood, which occurs, apparently, only in children of parents of Mediterranean, and particularly of Greek, Italian, or Syrian origin. It is characterized by mongoloid facies, splenomegaly and the presence of large numbers of erythroblasts in the circulating blood. Roentgenologic examinations of the bones show thickening of the flat bones of the skull, and more rarely, of the cortex of the long bones, with spicules arranged in fine radiating lines. The anemia is usually of severe grade, hypochromic in type, and associated with definite and often considerable leukocytosis. In our cases the average red blood cell count was about 2,500,000 and the leukocytes 10,000.

Splenectomy was performed upon four children, 19 months, and four, five, and eight years of age, two of whom were brother and sister. All were of Italian parentage. There were no operative deaths but two of the children have since died, one, eight months and one, two years after operation, of progressive anemia and pneumonia. The other two children are living, three and one-half and four years after operation, but both have erythrocyte counts of slightly over 3,000,000 cells, and hemoglobin values around 50 per cent. While

TABLE VII

PRE- AND POSTOPERATIVE BLOOD STUDIES AND RESULTS IN THREE PATIENTS SUBJECTED TO SPLENECTOMY FOR REFRACTORY PRIMARY ANEMIA

Case	Sex	Age	Major Complaint	Hemoglobin		R B C Count		W B C Count		Platelets		Follow-up	
				Preoper	Latest	Preoper Mil	Latest Mil	Preoper Thous	Latest Thous	Preoper Thous	Latest Thous	Duration	Result
M A	F	36	Hemorrhage	20	20	1 1	1 2	2 0		40		7 wks	Died
M S	F	39	Hemorrhage	34		1 6		2 0		42		9 days	Died
J B	F	59	Anemia	26	15	1 2	6	1 7		100		10 mos	Died

TABLE VIII

PRE- AND POSTOPERATIVE BLOOD STUDIES AND RESULTS IN FOUR PATIENTS SUBJECTED TO SPLENECTOMY FOR MISCELLANEOUS PATHOLOGIC

## CONDITIONS

Diagnosis	Sex	Age	Major Complaint	Hemoglobin		R B C Count		W B C Count		Platelets		Follow-up	
				Preoper	Latest	Preoper Mil	Latest Mil	Preoper Thous	Latest Thous	Preoper Thous	Latest Thous	Duration	Result
Nodular cirrhosis	M	12	Swelling of abdomen	70		3 2		9 0		170		3 days	Died
Leukemia	M	34	Weakness	30	35	1 6	1 8	1 5		135		4 mos	Died
Retothelial sarcomatosis	F	46	Weakness	62		3 2		4 0		220		8 hrs	Died
Nonlipoid histiocytosis	F	3	Purpura	80	79	3 9	3 0	2 9		50		6 mos	Died

it is possible that the lives of the last two children have been prolonged by operation, this is perhaps open to question (Table VI) All four cases showed the increased outpouring of nucleated red blood cells, recognized as being a characteristic effect of splenectomy in this condition

**REFRACTORY PRIMARY ANEMIA**—Although it is the universal opinion of hematologists and surgeons that splenectomy does not benefit patients with true aplastic anemia, this diagnosis is sometimes very difficult to establish, and in some cases of refractory primary anemia, the operation is sometimes resorted to in the hope that it may change the course of the disease This group as a whole has recently been discussed by Rhoads and Barker<sup>23</sup> Under these conditions, we have performed the operation in three such cases (Table VII), in one frankly as an experiment in a patient (M S) who was rapidly losing ground and in whom the course of the disease was in no way altered by the procedure She died nine days after operation from continued bleeding from the gums and vagina and with progressing anemia

When considering operation in the other two cases, we were influenced by the result obtained in one of the patients (E F) whom, because of his subsequent course, we have included in the group of thrombopenic purpura, although so far as his preoperative picture was concerned, his findings closely simulated those of the patients referred to here In neither of these two patients, however, was such a happy result obtained, for, while both appeared to derive temporary benefit and were able to go home and be up and about, both suffered a relapse and died, one, seven weeks, and one, ten months after operation

**MISCELLANEOUS CONDITIONS**—Splenectomy was also performed upon a child with nonlipoid histiocytosis, whose disease has been described from the pathologic standpoint by Foot and Olcott,<sup>24</sup> and whose subsequent course is appended

**Case Report**—A white female, age  $2\frac{3}{4}$  years, had had purpura for one year, the spleen was known to have been enlarged for three months prior to her first admission Blood studies showed a moderate anemia, red blood cells, 3,700,000, white blood cells, 3,900, with 80,000 platelets The liver and spleen were both considerably enlarged Two months later the platelets had fallen to 50,000 After two transfusions, splenectomy was performed The platelets rose after operation to 300,000 and she was discharged improved The improvement was temporary, however, and she was readmitted three months later with a recrudescence of the purpuric manifestations and a still greater enlargement of the liver She continued to run a low-grade fever until her death a few weeks later

*Autopsy*—*Anatomic Diagnoses* Healed splenectomy wound, moderate hyperplasia and hyperemia of the bone marrow, cysts of the intervertebral disks, petechiae in the skin over the trunk and in the epicardium, pericardial effusion, and granular degeneration of the tubules of the kidneys

*Microscopic Examination* showed (1) Notable increase in mononuclear phagocytes in the spleen and the lymph nodes of the peritoneal cavity and, to a lesser degree, in the bone marrow (2) The absence of demonstrable fat or lipins in the phagocytes (3) Simple cystic degeneration of the intervertebral disks

The operation apparently alleviated somewhat the discomfort caused by the spleen as a large abdominal tumor mass, and temporarily relieved the purpuric manifestations but did not arrest the progress of the disease

Splenectomy was also undertaken in a man, age 34, who survived the operation but was not improved, and at postmortem, four months later, was shown to have leukemia His subsequent course is appended

**Case Report**—A male, age 34, was admitted to the Hospital of the Rockefeller Institute, complaining of weakness and anemia of ten months' duration He had had psoriasis for which he had received roentgenotherapy for about five years On admission to the hospital he was pale and dyspneic The liver was palpable just below the costal margin, but the spleen could not be felt Blood studies showed a hemoglobin of 30 per cent, red blood cells, 1,600,000, white blood cells, 1,500, with 45 per cent reticulocytes Bone marrow biopsy showed a very cellular marrow with a distinct increase in primitive cells Abundant red cell formation was evident Studies of pigment output indicated increased hemolysis It was in the hope of decreasing this factor that splenectomy was undertaken He stood the procedure satisfactorily but was little improved He was given repeated transfusions and returned to his home He died four months after operation with progressive anemia At postmortem the normal structure of the bone marrow was found to have been completely replaced by cords and masses of round to oval cells with hyperchromatic nuclei and basophilic cytoplasm

One of the operations which terminated fatally was performed upon an Italian woman, age 46, whose symptoms consisted of weakness, anorexia, and vague, upper abdominal pain She had also had occasional attacks of nausea and vomiting Other than for the evident anemia and considerable enlargement of both the liver and spleen, physical examination was negative The blood findings were as follows Hemoglobin, 62 per cent, red blood cells, 2,900,000, white blood cells, 4,000, platelets, 200,000 Bleeding and clotting time, normal, Wassermann, negative, icteric index, 94 Roentgenologic examination of the chest and gastro-intestinal tract showed nothing abnormal

The preoperative diagnosis was Banti's disease, and splenectomy was performed without difficulty The patient reacted poorly after operation, however, and died eight hours later with hyperpyrexia Postmortem examination revealed retothelial sarcoma which had involved the spleen, liver, pancreas, kidney and mesenteric nodes

The other operative fatality occurred in an Italian boy, age 12, who had suffered from weakness, vague indigestion and frequent epistaxis for about six months Two weeks before admission to the hospital his abdomen began to swell and several purpuric spots appeared on his face

Physical examination on admission showed his abdomen to be markedly distended with fluid, and after paracentesis with the removal of 2,000 cc of clear, straw-colored fluid, the liver and spleen both became easily palpable Blood findings at this time were as follows Hemoglobin, 70 per cent, red blood cells, 3,200,000, white blood cells, 9,000, polymorphonuclears, 83 per cent, lymphocytes, 15 per cent, reticulocytes, 2 per cent, platelets, 170,000,



icteric index, 25 Roentgenologic examinations of the chest and gastrointestinal tract revealed nothing pathologic

Following the first paracentesis, the child became jaundiced, the anemia became more marked, and the fluid reaccumulated rapidly. A fatal outcome was obvious and splenectomy was undertaken as a last resort. The jaundice increased rapidly, however, after operation and the patient died with cholemia three days later. *Postoperative Diagnosis* Nodular cirrhosis

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DISCUSSION—DR ALLEN O WHIPPLE (New York) said that he had had the opportunity of reviewing Doctor Andrus' cases in some detail and that his experience at the Presbyterian Hospital had been quite similar to that of Doctor Andrus, as regards the indications for and the results of splenectomy. There had been no deaths following the operation for hemolytic jaundice and none of the patients, operated upon for typical idiopathic thrombocytopenic purpura, had been lost. In a total of 130 splenectomies, 34 were for hemolytic icterus, 21 for idiopathic purpura, and 53 were cases of so-called Banti's syndrome. The poor results occurred in the last named group although there were in it, also, some remarkable results that cannot be explained.

Hemolytic icterus or the typical spherocytic jaundice is a definite, clear-cut syndrome and one in which splenectomy gives brilliant results. Doctor Whipple said the feeling at Presbyterian Hospital is, increasingly, to regard the presence of spherical microcytes as absolutely essential to diagnosis, plus increased red blood cell fragility. These two criteria must be present before a case is called typical hemolytic jaundice and spherical microcytes are re-

garded as more important than fragility. The group characterized by lack of spherocytes should be very carefully differentiated from typical spherocytic jaundice, because in it the results are very poor. Some cases are difficult to differentiate (typical round microcytes were found in none of the cases studied, although some had a variable red cell fragility). Differentiating these two groups is particularly important so far as therapeutic results and indications for surgery are concerned.

Idiopathic thrombocytopenic purpura should also be classified into typical and atypical thrombocytopenic purpura. "Idiopathic" implies that the cause is not quite known, but there are certain etiologic factors, such as infections, both acute and chronic, among which is tuberculosis, sometimes associated with purpura. Certain metallic poisons are also, sometimes, associated with it and some cases of aplastic anemia are very difficult to differentiate and recognize. If these conditions are ruled out and if the patient, after a thorough trial with conservative measures, still continues to show a tendency to bleed, splenectomy does give very excellent results.

In regard to Banti's syndrome—a term used probably because it covers a certain amount of ignorance—certain interesting factors are known to be present. Some of the Banti's cases are undoubtedly due to splenic or portal vein thrombosis. Doctor Whipple cited three in which the history of trauma was very definite and resulted in thrombosis of either the splenic or of a large portal area which caused engorgement of the splenic circulation and resulted in splenomegaly. Splenectomy in all three was followed by very excellent results. Another feature Doctor Whipple said he had noted, after checking up more than 20 cases, was that the splenic vein pressure is sometimes increased 300 to 500 per cent above normal. These pressures were taken at the time of operation and compared with the peripheral circulation pressure. The splenic vein pressure proved to be astonishingly high in cases of portal block.

Another group of cases is represented by schistosomiasis, many cases coming up from Porto Rico, Venezuela and other parts of the world, where *Schistosoma mansoni* is endemic. This reproduces Banti's syndrome in every detail. Doctor Rousselot of the Presbyterian Hospital staff has been working on the problem for two years and expects to publish his results shortly. By means of injecting salicylate particles into the portal circulation over a period of months, that is, at intervals of four months or so, he has been able to reproduce a typical and absolutely characteristic picture of Banti's disease in the dog. The pathologic findings have been characteristic, namely, esophageal varices, enlarged spleen, marked cirrhosis, and engorgement of the portal circulation.

Finally, Doctor Whipple said, in connection with idiopathic purpura cases, that the capillary fragility is felt to be more important even than the platelet count, as a result of the studies of Doctor Elliott of his staff. He studied this in a very large series of cases, both operated and nonoperated, and in a control series, using the Dollendorf apparatus, which registers pressure much more accurately than the tourniquet, he found that increased fragility was much more constant than the platelet count as a manifestation of purpura. Very quickly—within five or ten minutes after splenectomy—there was found to be a return to normal in the capillary fragility, if tested by that apparatus.

DR PAUL REZNIKOFF (New York) said that it was quite apparent from the cases presented that the conditions under discussion really affect the spleen incidentally. The physician or surgeon is confronted with general medical and surgical diseases and only in traumatic conditions, and perhaps tumors of the spleen, are local splenic abnormalities found. The significance of this

is that the blood and other parts of the body, and most important, the patient, must be studied intensively

Two points about spherocytic or hemolytic jaundice were particularly discussed by Doctor Reznikoff. He expressed the belief that the real lesion is a spherocytosis, a microcyte which is globular rather than of the biconcave shape of the normal cell. The cell, being globular, cannot imbibe water as well as the biconcave cell or have the room to swell, and that explains its apparent fragility or decreased resistance to hypotonic saline. It is very simple to measure the spherocyte. The simplest way is with the micromanipulator. With these cells in a hanging drop one can see, as the cell is turned over, that it is a sphere. If not available, a good indirect way is to measure the diameter of the cells, presumably in a fresh drop, in which the diameter is usually below seven micra, often below 6.5. Then by doing an hematocrit reading one gets a surprisingly high cell-pack for that diameter which gives, in an indirect way, evidence of spherocytosis.

Another very important point in questionable cases of hemolytic or spherocytic jaundice is that many of these patients do not show all the essential criteria. Some show very little. For example, Gannslen, in describing 105 cases, reported that 10 per cent showed no change to fragility, 35 per cent no anemia, 30 per cent no splenomegaly, and 40 per cent no jaundice. Doctor Vaughan by bringing in all the relatives that she could obtain—fathers, mothers, aunts, sisters, brothers and cousins—found a very clear-cut result. A very high proportion of the relatives had abnormal red blood cells, as judged by the hypotonic saline test when the patient may not have had this. In this way she has thrown doubt on acute hemolytic anemia as a separate entity. Even though anemia, jaundice, or complaints were absent, the relatives having no complaints, there may still be marked fragility or decreased resistance to hypotonic saline.

Thrombocytopenic purpura is a disease which gives hematologists a great deal of trouble. It is not easy to differentiate from other conditions such as aplastic bone marrow, which is really aplasia of the entire bone marrow, or acute leukemia. Sometimes it is impossible to know what the patient had even after autopsy. However, while the platelets are reduced in all these conditions and, while in all, anemia is present as a rule, it is usually in thrombocytopenic purpura that the patient has no real leukopenia. These patients usually have some leukocytosis and quite a representative percentage of polymorphonuclear cells, most of which are fairly immature. That is an important distinction. Another distinction, not as good a guide, but helpful, is that while capillary fragility is an important factor in thrombocytopenic purpura it is also a very troublesome thing in acute leukemia and in the so-called aplastic anemias. But in thrombocytopenic purpura the patient almost invariably has very poor clot retraction and a very fragile clot. At the end of 24 hours it will come apart if picked up with the needle. This is true, also, of many other conditions, including acute leukemia and in the aplastic bone marrow conditions, but not quite so true. If one obtains a firm clot and good retraction it speaks against thrombocytopenic purpura. These points all have to be evaluated and sometimes, even then, it is extremely difficult to distinguish between these conditions.

Regarding Doctor Andrus' patient E. F., Doctor Reznikoff said it was reasonably certain that he had a leukopenia, an anemia, thrombocytopenia, capillary fragility, poor blood clot retraction, and a fragile clot, but the striking features were the marked leukopenia and thrombocytopenia. It was thought that there was aplasia of the bone marrow. In desperation, the spleen was removed, with a surprising result still not understood. The patient

has never had a normal platelet count, the highest being 175,000. He is not bleeding, can work, and has a fairly normal red blood cell count.

The argument against operation in patients with acute thrombocytopenic purpura is that there is a very high mortality rate. Doctor Reznikoff's impression from the literature and his own experience is that if one does not operate the mortality rate is even higher. With adjuvants such as transfusion, it is usually desirable to operate.

Doctor Whipple spoke of the miracle of removing the spleen and seeing the purpura disappear within five or ten minutes. Doctor Reznikoff said that it was a miracle to him to see all the bleeding stop as the pedicle is clamped. That is what happens in acute thrombocytopenic purpura. Some of these patients who take sedormid will confuse one because of having a picture a good deal like thrombocytopenic purpura, but not usually with a very low platelet count.

Doctor Reznikoff called attention to the important fact that Doctor Patek, in the Research Department of the Hospital for Chronic Diseases, is getting some very interesting results in cirrhosis of the liver with vitamin B<sub>1</sub> therapy. If the work bears the fruit it promises, surgeons are going to be requested to remove more spleens both in Banti's disease and in cirrhosis of the liver, as an adjuvant to the vitamin B<sub>1</sub> therapy. There is no question that the splenomegaly puts a tremendous load on the liver. If Doctor Patek's work is successful, splenectomies will have to be increased. It will be more difficult to cure the cirrhosis if the spleen is left in.

If a patient comes in with suspected Banti's disease, it is important to appreciate that in the typical case the blood picture as a rule shows a leukopenia and thrombocytopenia to some degree, not marked, but certainly below 200,000 with a slight increase in the resistance to hypotonic saline, and, also, in most cases where the liver is involved, a macrocytosis. In about one-third of the cases of Banti's disease there is really a macrocytic anemia.

It would be very satisfactory if one could associate an increased platelet count, after splenectomy, for instance for Banti's disease, with thrombosis, but the majority of reports, especially the very good cases described by English authors, show that the two cannot always be associated. Thrombosis may occur with a fairly low platelet count and very often thrombosis will not occur in counts of one million or above. This is true also of a low platelet count in thrombocytopenic purpura. Formerly it was taught that if the platelet count falls below 100,000 that is the bleeding point. But many patients have been seen with 20,000 or 30,000 platelets without bleeding and with 150,000 platelets with bleeding. As yet the relationship between platelet count and purpura is not understood.

Doctor Reznikoff, in closing, stressed the fact that medical men tend to urge splenectomy when they reach the end of their rope, and the surgeon asks the medical man to give a good reason for it. His experience has been that the best results have occurred when the surgeon has known a good deal about his work and has questioned him, and particularly when there has been good cooperation and frank criticism between the surgeon, the medical men and the hematologist.

# A METHOD FOR TRANSPLANTING THE ADRENAL GLAND OF THE DOG WITH REESTABLISHMENT OF ITS BLOOD SUPPLY\*

## REPORT OF OBSERVATIONS

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A SEARCH of the literature reveals no instances in which the adrenal gland has been transplanted in toto with the reestablishment of its blood supply by suture of blood vessels. A number of investigators have placed parts of an adrenal gland in various sites in the body and have obtained evidence subsequently of viability of the cortical tissue. Most of the work on the grafting of adrenal tissue has been performed on rabbits, rats and guinea-pigs. There is no convincing evidence that grafting has been carried out successfully in dogs. Blodinger, Klebanoff and Laurens<sup>1</sup> obtained no evidence of function in autoplasmic and homoplasmic transplants in the dog. The animals died soon after removal of the second gland in spite of transplantation, and the transplants had degenerated by the thirty-fourth day. Crowe and Wislocki<sup>2</sup> have the following to say concerning their experiments on dogs: "An autoplasmic transplantation of a fragment of adrenal may 'take' but is of no functional value. When a fragment of adrenal containing both cortex and medulla is transplanted, the cortical cells may survive, but the medullary cells are absorbed." The procedure of Haberer<sup>3</sup> did not result in a true transplantation of adrenal tissue. The adrenal gland was freed of its peritoneal attachments and was placed in an incision in the kidney. The blood vessels to the gland were left intact.

The method herein described was developed primarily in order to determine the effect on experimental hypertension due to renal ischemia resulting from the removal of one adrenal and of the denervation of the remaining one by transplanting it to the neck. These studies will be reported subsequently in a paper dealing with hypertension. This method of transplanting the adrenal to the neck seems to offer advantages in certain types of studies in that it is a denervated preparation, its venous return is through the external jugular vein which is located just beneath the skin and can be punctured without difficulty, and the superficial position of the gland makes it readily accessible for roentgen treatment, removal under local anesthesia or for other procedures.

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The purpose of this paper is to describe the method of transplantation and to report a few studies on this preparation

METHOD—The principle of the method consists of utilizing the vessels in the pedicle of the kidney for the flow of arterial blood to the adrenal and the return of venous blood from it. There are at least several arteries supplying the adrenals, and these are derived from the aorta, the inferior phrenic and the renal arteries. Most of the venous return is through the adrenal vein which usually empties into the inferior vena cava, but occasionally, on the left, it opens into the renal vein. In addition, there are smaller veins, some of which join the renal. The adrenal vessels are too small for direct anastomosis to other vessels. Hence the adrenal was removed in mass together with the kidney and its pedicle, and the renal artery and vein were anastomosed to the carotid artery and external jugular vein. A method similar to this was employed by Dederer<sup>4</sup> in one experiment in which homotransplantation of a kidney and ovary was performed. The principle of the method is somewhat different from that of the mass transplantation of organs as employed by Carrel.

Large, mature dogs were used in all experiments. In most instances, the blood pressure was determined by the needle puncture method for a number of days preceding the operation. Employing aseptic technic and general anesthesia, the left kidney and adrenal were exposed through an incision in the left flank. Two persons usually carried out this procedure while a third prepared the vessels in the neck for the anastomoses. Beginning at the upper pole of the left adrenal, the gland was freed, care being taken to ligate the vessels and not to enter the capsule. It is particularly important not to disturb the connections between the adrenal and the pedicle of the kidney during the freeing of the rest of the gland. These connections are shown in Figure 1. In most instances, the main adrenal vein joined the inferior vena cava. Since ligation of this vein usually resulted in a good deal of venous engorgement of the adrenal, it was postponed as long as possible. After having completely freed the adrenal except for its attachments to the renal pedicle, the ureter was cut across, and renal artery and vein were ligated and divided as close to the aorta and inferior cava as possible. This allowed the removal of the kidney and adrenal in one mass. The renal artery was then anastomosed to the proximal end of the carotid artery and the renal vein to the proximal end of the external jugular vein using the method of Carrel. In a few instances, the kidney was removed after having completed the anastomoses, the vessels being ligated and divided just at the hilus. This left a considerable length of renal artery and vein from which the adrenal might receive its blood supply. In most instances, the kidney was placed together with the adrenal in a pocket beneath the skin in the neck and the tip of the ureter was brought out through a stab wound in the skin. The incisions in the neck and flank were closed. The length of time that the transplanted tissues were completely deprived of their circulation varied from 29 to 42 minutes in the different experiments. The animals were given the usual kennel diet

of meat and chow and were not administered supportive or substitution ad-renal therapy

*Observations*—Transplantations were performed on 14 dogs. Seven of these were successful in that subsequent removal of the other adrenal was not followed by deleterious effects. The seven failures were due to thrombosis of the vessels, necrosis and infection of the tissues of the neck, distemper, secondary hemorrhage or to adrenal insufficiency. A further analysis of the failures is of interest. In four of these seven experiments, the kidney was removed immediately after the anastomosis of the vessels. In three of the four experiments in which the kidney was removed immediately, marked discoloration of the skin overlying the transplant occurred several days later and this was followed by massive infection and necrosis. In two of the



FIG 1—Drawing showing the kidney, the adrenal, the tissues connecting the two, the renal artery, vein and ureter

three failures in which the kidney was transplanted together with the adrenal, the opposite adrenal had been removed previously. It follows that a failure resulted in only one experiment in which the kidney and adrenal were transplanted to the neck of a dog in which the other adrenal had not been removed. Secondary hemorrhage caused the death of this animal.

The remaining observations are concerned with the favorable transplants. As has been stated, seven of these were entirely successful. In six of the seven, the kidney was transplanted with the adrenal and was not removed until some time later. The interval separating the operation and the removal of the transplanted kidney varied from eight to 93 days in the six experiments, the individual days being eight, 32, 39, 68, 71 and 93. There was evidence of renal function, although suppressed, in all instances at the time of removal of the transplanted kidney. In the remaining experiment, the

## TRANSPLANTATION OF ADRENAL GLAND

kidney was removed immediately after having anastomosed the vessels. In six of the seven animals, the nontransplanted adrenal was removed after intervals varying from 13 to 32 days following the transplantation of the other gland. The individual times were 13, 14, 18, 21, 26 and 32 days. In the remaining animal, the right adrenal gland was removed 13 days prior to transplanting the left gland to the neck. No evidence of adrenal insufficiency was observed. It is of interest that the main adrenal vein in this animal emptied into the renal rather than into the inferior vena cava as was usually the case. It is our impression that the percentage of successes would have been higher had this been the situation in all instances.

The condition of the animals did not seem to be altered by the removal



FIG 2 —Reading left to right: Mother (seven months' transplant), daughter (age five weeks), and father (six months' transplant).

of the right adrenal following the transplantation of the left adrenal gland. They ate heartily and maintained their weights. The general appearance was the same as before the operation. If disturbed by another dog while eating, such an animal would growl and fight. There was no evidence of a decrease in their ability to withstand exposure to cold. Although exposed at times to other dogs with distemper, none of them contracted it. One of the animals gave birth to a single normal puppy seven months following transplantation of the adrenal or 65 months following the removal of the other adrenal. The puppy fed from the breast and developed normally. A photograph of the puppy together with the parents is shown in Figure 2. The father of the puppy had been subjected six months previously to transplantation of one adrenal. This is the animal in which the right adrenal was removed 13 days prior to transplanting the left one. One animal, which was received from the city pound, has been returned to his original owner. No alteration in the behavior of the dog has been observed. It is



now six months since the transplantation of the left adrenal to the neck and 55 months since the removal of the right adrenal. Three dogs were doing quite satisfactorily after intervals of three months, 45 days and 37 days following the removal of the right adrenal and a slightly longer time following the transplantation of the left one. They were used at that time for a study of the effects of renal ischemia on the blood pressure. The results will be reported elsewhere but it may be stated that a response identical to that in dogs with intact adrenals was obtained. The findings at autopsy in these animals will be described in a subsequent paragraph.

In one experiment, the survival period of the animal following the removal of the transplant under a local anesthetic was determined. The operation was performed six months following the transplantation of the left adrenal or 55 months after the removal of the right adrenal. The transplant appeared essentially normal grossly at the time of its removal. The animal was fed the same diet (meat and chow) following the removal of the transplant as he had been given previously and no supportive or substitution adrenal therapy was administered. Very little food was taken after the first 36 hours. Rather much to our surprise, death occurred slightly less than five days following the removal of the transplant. There was a decline in the arterial blood pressure (needle puncture method) from 165 Mm Hg prior to the removal of the transplant to 157 at the end of the first day, to 125 on the second, 115 on the third and to 82 Mm Hg on the fourth. The animal died less than 24 hours subsequently. Similarly the total blood chlorides declined somewhat from the control of 495 mg per 100 cc to 486 on the first postoperative day, 462 on the second, 453 on the third and 412 on the fourth day. The autopsy was essentially negative. No accessory adrenal tissue was found in the neck or in the lumbar region. The thymus was definitely enlarged. Microscopic studies on the transplanted adrenal will be described later.

The arterial blood pressure of three of the animals became somewhat elevated following the transplantation of one adrenal and the removal of the other one, while there was no change from the preoperative level in the remaining four dogs. It is to be remembered that the right adrenal was removed from a site near the remaining kidney and this procedure in itself is followed at times by the formation of a good deal of scar tissue in the neighborhood of the renal artery. It seems possible that this may have resulted in some ischemia of the kidney with an associated rise in blood pressure.

As has been stated, the venous return from the transplanted adrenal was through the left external jugular vein. The superficial position of this vein makes it readily accessible for puncture with a needle and hence blood may be withdrawn from it. The oxygen content of this blood as well as that withdrawn from the opposite external jugular vein and that obtained from an artery was determined. Blood was withdrawn under oil and the oxygen content was determined by the Van Slyke-Neill method. From

these figures, the arteriovenous difference in oxygen was determined. This oxygen content of blood from the left jugular (transplant) was definitely higher in all experiments and hence the arteriovenous difference in oxygen was smaller. These figures are contained in Table I. We were desirous of measuring the rate of blood flow also but this would have endangered the preparation and it was not done.

TABLE I  
OXYGEN CONTENT OF BLOOD OF RIGHT AND LEFT (TRANSPLANT) EXTERNAL JUGULAR VEINS

Dog No	Oxygen Content Vols Per Cent		Av Dif O <sub>2</sub> (Adrenal)	Opposite Jugular O <sub>2</sub> Vols Per Cent	Av Dif O <sub>2</sub> (Nontransplant)
	Arterial	Left Jugular (Adrenal)			
30	20.62	18.66	1.96	13.98	6.64
55	18.27	16.97	1.30	16.58	1.69
60	16.55	14.58	1.97	10.72	5.83
56	17.29	16.71	0.58	11.92	5.37
59	14.81	13.28	1.53	11.05	3.76
21	13.91	12.72	1.19	8.47	5.44
28	8.04	6.88	1.16	5.14	2.90

Efforts were made to determine whether or not there was epinephrine in the venous blood from the transplant. This was obtained by puncturing the left external jugular vein, and clotting was prevented by the use of heparin. The method followed was that employed by Suguwara<sup>5</sup> in which a segment of intestine from the rabbit is exposed to the solution to be tested. Many tests were made on blood samples obtained from four of the dogs with a transplant. Specimens of blood were obtained on one occasion after massage of the adrenal gland and on another following the intravenous administration of 4 mg of acetylcholine. The responses of the intestinal strip to these samples of blood were compared to the effects of blood withdrawn from the opposite external jugular vein and to the effects of dilutions of a standard solution of epinephrine hydrochloride made up by weight from pure crystals of epinephrine. The intestinal strips responded readily to dilutions of the latter solution of one part in 25 million. In no experiment was there an unequivocal inhibition of the intestinal strip by venous blood from the transplant. The response in most instances was practically identical to that of blood obtained from the opposite external jugular vein. We do not feel positive as a result of these tests that epinephrine was not present, but certainly its presence was not demonstrated.

In one experiment only, samples of blood from the two external jugular veins were injected into a rat by Dr. John Williams and the effects on the blood pressure were observed. Each injection caused a rise in blood pressure, but the pressor response was greater following the introduction of venous blood from the transplant.

The effects on the blood sugar of massage of the transplanted adrenal

and of the intravenous injection of epinephrine were determined in two experiments. The adrenal had been transplanted about eight months previously in one of the animals and six months in the other. Samples for blood sugar determinations were withdrawn from the femoral vein, and epinephrine was introduced into this vein. The results were practically identical in the two experiments, one of which is as follows. A few minutes after having placed the animal on the table, the blood sugar was 74 mg per 100 cc. The transplanted adrenal was then massaged gently for 25 minutes. Immediately after completing the massage, the blood sugar was 70, it was 75 three minutes later and 80 ten minutes later. One-half cubic centimeter of 1:1,000 epinephrine was then injected. The blood sugar was 74 mg one minute following the injection and 105 mg five minutes after the injection.

Three of the animals are alive at the time of the writing of this paper and they will be observed for a longer period of time. The transplants can be palpated in the neck and a pulsation in the carotid artery to the adrenal can be felt. It has been approximately seven months, eight months and nine months since the nontransplanted adrenals were removed from these three dogs. Three of the remaining four dogs were used for a study on hypertension. The transplants were removed after three months in one instance, 55 days in one and 45 days in the other following the excision of the nontransplanted adrenal. The transplant was removed from the remaining dog 55 months after having taken out the other adrenal, and the survival period of the animal was determined. The transplants of these four animals were easily identified at the time of their excision and they appeared essentially normal. The carotid artery to the transplant was patent and bright blood ran from the distal end of the external jugular vein when it was divided. The adrenal gland was approximately the same size as it had been at the time of its transplantation. When the adrenal was cut across, cortex and medulla could be identified on gross examination. The autopsies showed no definite abnormality except for enlargement of the thymus and lymph nodes in the animal in which the transplant had been removed five days previously. Examination of the adrenal areas did not reveal any gross evidence of accessory adrenal tissue. These areas were removed in mass for microscopic study and no cortical cells, exhausted or otherwise, were found.

The points of interest on microscopic examination are limited to the transplanted tissues. As stated, four transplants were studied, the length of time separating the transplantation and the removal of tissue for examination being 193, 116, 88 and 66 days. The findings on microscopic study were practically identical in the four experiments. The cells of the cortex and medulla appeared normal. A low power view showing the cortex and medulla of the transplant of 88 days' duration is given in Figure 3. A higher magnification of the cells in the medulla is given in Figure 4. The adrenal in this instance was removed 193 days following the transplantation. A pyridin silver stain showing unmyelinated fibers in the cortex of the

# TRANSPLANTATION OF ADRENAL GLAND

88-day transplant is shown in Figure 5. A similar stain showing nerve fibers with end bulbs in the medulla of the same adrenal is contained in Figure 6. A low power view of the 66-day transplant stained with osmic acid is shown in Figure 7. No definite granules were observed in the medulla. Figure 8 shows a low power view of the 193-day transplant together with an adjacent ganglion stained with pyridin silver. A ganglion with its nerve, part of the cortex and blood vessels of the 88-day transplant are pictured in Figure 9. A higher magnification of part of a ganglion and the nerve of the 116-day transplant is shown in Figure 10. Some of the ganglion cells appear entirely normal while others have eccentric nuclei.

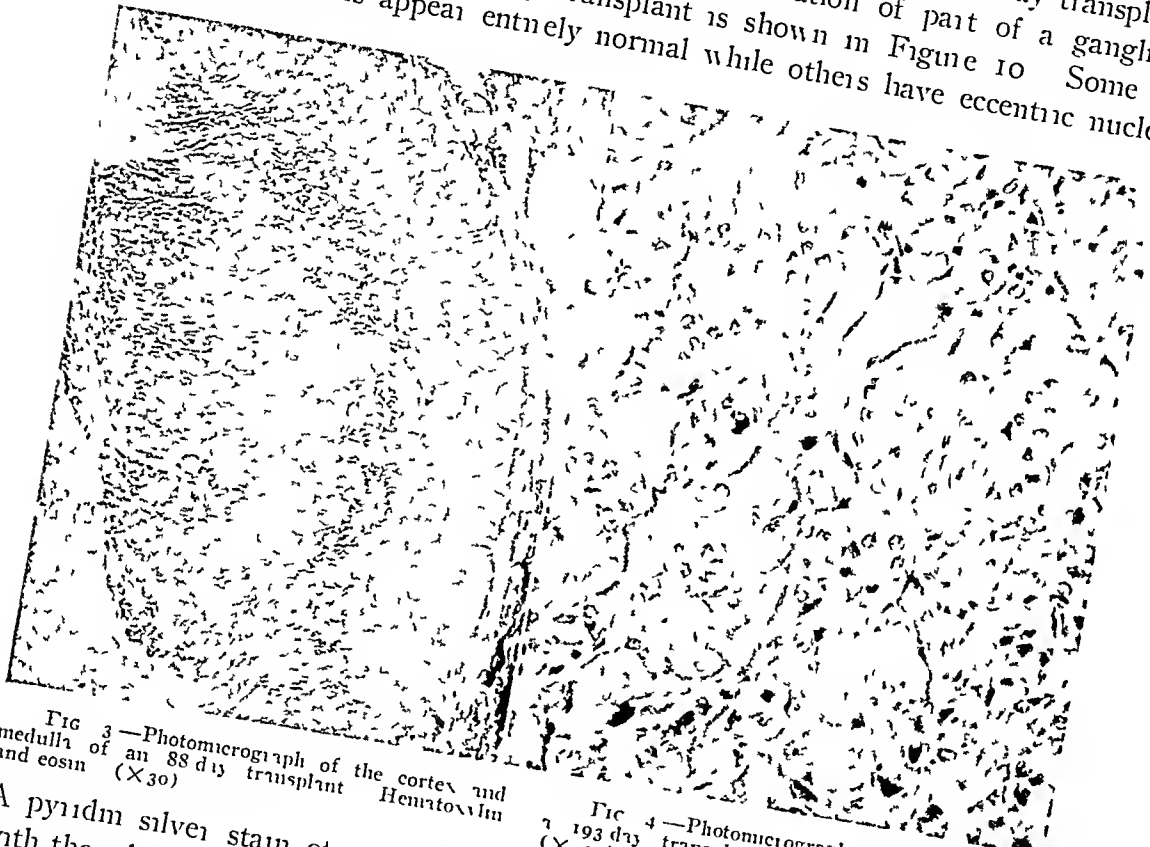


FIG 3—Photomicrograph of the cortex and medulla of an 88 day transplant Hematoxylin and eosin (X30)

FIG 4—Photomicrograph of the medulla of a 193 day transplant Hematoxylin and eosin (X500)

A pyridin silver stain of a ganglion which had been transplanted together with the adrenal for 193 days is shown in Figure 11. Several ganglion cells and nerve fibers are to be seen. Two of the four specimens fixed with Zenker's solution showed a suggestive chromaffin reaction.

**Discussion**—The method used in these experiments for transplanting the adrenal is one which may be employed for the transplantation of other organs in which the blood vessels are too small for anastomosis by suture. To reiterate, there are small vessels in the mass of tissue which connects the adrenal gland to the renal pedicle and these vessels convey sufficient blood to and from the adrenal when the renal artery and vein are connected to similar vessels in the neck. The survival of the animal in which the right adrenal was removed 13 days before the left was transplanted indicates that these vessels may be competent for adequate circulation from the outset. Halsted<sup>6</sup> noted in his experiments in which the parathyroids were trans-

planted, without blood vessel anastomoses, that a physiologic deficit was necessary for a successful "take." He stated "The autotransplantation of parathyroid glands into the thyroid gland and behind the musculus rectus abdominis has been successful in 61 per cent of the cases in which a deficiency greater than one-half has been created. In no instance has the autotransplantation succeeded without the creation of such deficiency." The right adrenal was not removed until approximately one month following the transplantation of the left one in some of the experiments, and yet the transplants functioned sufficiently to maintain life.

Crowe and Wislocki<sup>2</sup> placed fragments of adrenals of dogs in muscle and



FIG 5—Photomicrograph showing the unmyelinated fibers in the cortex of an 88 day transplant, treated by Ranson's pyridin silver method (X650)



FIG 6—Photomicrograph showing the unmyelinated fibers with end bulbs in medulla of an 88 day transplant. Pyridin silver. Oil immersion (X1500)

subsequently noted viable cells of the cortex, but no medullary cells were to be seen. The grafts did not maintain life when the adrenal tissue elsewhere was removed. They state "The only explanation we can offer for the failure of the above experiment is that the engrafted fragment of adrenal was deprived of its normal nerve supply." Grollman<sup>7</sup> states "The medullary tissue shares the property of nervous tissue generally, to which it is embryologically related, in showing little or no regenerative capacity." As has been stated, the medullary tissue in our transplants appeared essentially normal.

It is of interest that a massive discoloration and necrosis of the skin occurred in a number of the experiments in which the kidney was not transplanted together with the adrenal. It seems likely that the removal of the kidney at the time of the transplantation may result in a less adequate blood supply to the adrenal. The discoloration may be due to the escape of

dopa or epinephrine into the tissues. A number of investigators have commented upon the irritating properties of medullary tissue. Jaffe<sup>8</sup> carefully removes the medulla prior to transferring cortical tissue to the muscle of the abdominal wall. Grollman<sup>7</sup> states "Undoubtedly the liberation of epinephrine from the degenerating medulla will inhibit growth of the cortical cells and hence one should only use the outer zone of the cortex (which constitutes the active regenerative tissue) in transplants." Our results are not strictly comparable to those cited because of the difference in the technic of transplantation.



FIG 7—Photomicrograph showing the cortex and medulla of a 66 day transplant. Osmic acid stain ( $\times 100$ )



FIG 8—Photomicrograph of the cortex, medulla and adjacent ganglion in a 193 day transplant. Pyridin silver ( $\times 50$ )

The length of time that the adrenals were completely deprived of blood supply during the transplantation varied from 29 to 42 minutes. This is almost certainly a longer period of anoxemia than would be tolerated by the brain or heart. Lawen and Sievers<sup>9</sup> found in experiments on rabbits that complete obstruction of the pulmonary artery and aorta would result in death after lasting more than two and one-half minutes. However, the animals could be revived by the aid of different types of resuscitative measures even if the obstruction had been eight minutes in duration. Nystrom and Blalock<sup>10</sup> found in experiments on dogs that approximately 11 minutes was the maximum time that complete occlusion of the pulmonary artery might be followed by recovery.

The blood returning from the transplanted adrenal had a very high oxygen content and hence the arteriovenous difference in flow was quite small. Neumann<sup>11</sup> found the blood flow of the adrenals to be greater per gram of

tissue than that of any other organ. Even though the arteriovenous difference in oxygen is the smallest that we have encountered in observations on many of the organs of the body, the rapid blood flow suggests that the oxygen consumption per unit of tissue is not extremely small.

As stated, a positive test for epinephrine in the blood from the transplant by the intestinal strip method was not obtained. Grollman<sup>7</sup> states "It has been found that epinephrine is detectable in the blood of the adrenal veins so long as the nerve supply to the gland is intact. There is thus presumably a steady secretion of epinephrine into the circulation. The exact amount of this secretion has been a matter of controversy." Feldberg and his collab-

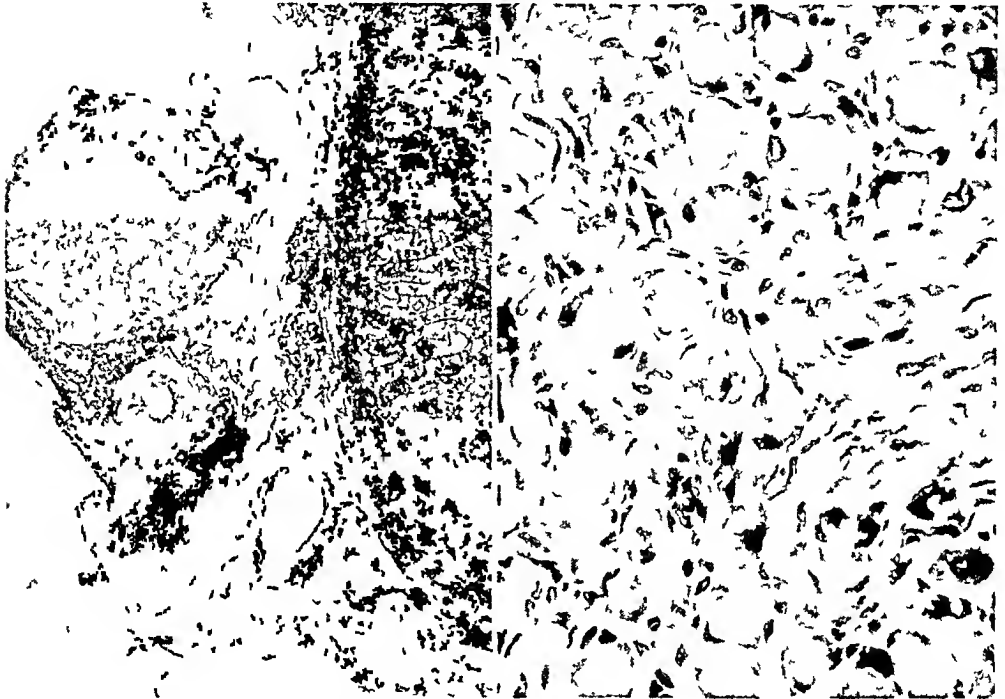


FIG 9—Photomicrograph of a ganglion with nerve blood vessels and cortex of adrenal in an 88 day transplant. Hematoxylin and eosin (X62)

FIG 10—Photomicrograph of the ganglion cells and nerve in a 116 day transplant. Hematoxylin and eosin (X550)

oratois<sup>12</sup> state that acetylcholine is the humoral transmitter of splanchnic impulses to the medulla. In our denervated preparations, the intravenous injection of acetylcholine did not result in a positive test for epinephrine in blood from the transplant. Epinephrine is known to exert a marked hyperglycemic activity. Massage of the transplant did not result in a significant alteration in the blood sugar in our experiments. De Takats and Cuthbert<sup>13</sup> noted that denervation of the adrenal decreases the hyperglycemic response to the injection of epinephrine. There was not a marked elevation in the blood sugar following the injection of epinephrine in our experiments. There is some doubt as to whether or not the medullary cells of our specimens exhibited the chromaffin reaction. Two specimens fixed with Zenker's solution showed a suggestive reaction and two others did not. It is said that

the chromaffin reaction may be absent in some instances despite the presence of epinephrine. Sections of two specimens stained with osmic acid showed no definite granules in the medulla. These findings together with our inability to demonstrate positively the presence of epinephrine by the intestinal strip method suggest strongly that the medulla contained little if any of this substance.

It is well known that untreated dogs rarely survive for more than a few days following bilateral adrenalectomy. There has been a great deal of controversy in the literature as to the reasons for the differences in survival periods as obtained by various observers. One group maintained that their longer survival periods were due to increased skill in the performance of the operation. In a two stage operation performed under ether anesthesia, Rogoff and Stewart<sup>14</sup> found an average survival period of approximately seven days, two of their animals living for 15 days. As has been stated, the survival period of one of our animals was determined following the removal of the transplant under local anesthesia, no supportive or substitution therapy being given. The transplantation of one adrenal and the removal of the other one had been performed about six months previously. Despite the fact that the animal appeared entirely normal at the time of the removal of the transplant under local anesthesia, death occurred slightly less than five days subsequently.

It is of interest that renal ischemia results in hypertension in animals with a single denervated transplanted adrenal. This point will be commented upon elsewhere.<sup>15</sup>

As has been stated, some of the cells of the ganglia transplanted together with the adrenal were entirely normal. The longest time separating the transplantation of the tissue and its removal for examination was six months and five days. Ranson<sup>16</sup> noted the survival for about 30 days of cells of the transplanted spinal ganglion of the rat. Clark<sup>17</sup> observed in dogs and cats normal visceral neurons which had been without the influence of the central nervous system for more than two years. Ward<sup>18</sup> transplanted lumbar sympathetic ganglia of the cat, and nerve cells were identified as long as 287 days after the grafting operation. In view of these results which were obtained without artificial reestablishment of the blood supply to the ganglia, it is not surprising that many of the ganglion cells were entirely normal in our experiments.



FIG. 11.—Photomicrograph of the ganglion cells and nerve fibers in a 191 day transplant. Pyridin silver. Oil immersion. ( $\times 1260$ )



Only unmyelinated nerve fibers were found in the transplanted adrenals in our experiments. Elliott<sup>19</sup> found that section of the splanchnic nerves causes the myelinated fibers of the adrenal gland to degenerate up to their endings in the medulla. This was interpreted as indicating that chromaffin tissue is innervated by preganglionic rather than by postganglionic fibers. Clark<sup>17</sup> commented upon the small ganglia which are found in the capsule of the adrenal and the nerve cells in the medulla, and he suggested that the numerous nerve fibers present in the adrenals of animals surviving a thoracolumbar ganglionectomy might be due to the presence of nerve cells in and adjacent to the glands. It seems most likely that the nerves observed in the medulla in our transplants arose from intrinsic ganglion cells. Hollinshead,<sup>20</sup> using cats, found that all the myelinated fibers underwent degeneration and the medullary plexus disappeared after removal of the upper lumbar sympathetic trunk in addition to section of both splanchnics. Unmyelinated fibers persisted in the gland after carrying out these procedures and also after careful denudation of the gland. Hollinshead<sup>20</sup> stated that these unmyelinated fibers apparently arise from the ganglia of the adrenal plexus, including the ganglia occasionally embedded in the capsule of the gland, and that their destination appears to be primarily the blood vessels of the gland. It was concluded that the chief innervation of the chromaffin cells contained in the medulla of the gland is preganglionic in nature. According to Hollinshead, the fibers to the adrenal traverse ventral roots of spinal nerves and reach the gland primarily through the lesser splanchnic nerve and through direct branches from the lumbar sympathetic trunk, and they end among the medullary cells without the interposition of postganglionic neurons. Transplantation of the adrenal in our experiments resulted in a persistence of the unmyelinated fibers and a degeneration of the myelinated ones as was found by Hollinshead when both splanchnics were divided and the lumbar sympathetic trunk was removed. Hollinshead and Finkelstein<sup>21</sup> found regeneration of nerve fibers to the adrenal following removal of the lower thoracic and upper lumbar sympathetic chain. "The regenerating fibers arose from the lower thoracic and upper lumbar spinal nerves and provided the gland with an apparently normal innervation as early as the fourth month after operation." As has been stated, only unmyelinated nerves have been found in our experiments in adrenals transplanted to the neck.

#### SUMMARY

A method is described for transplanting the adrenal gland to the neck of the dog. Since the blood vessels of the adrenal are too small for anastomosis by suture, the renal artery and vein of the adjacent kidney have been utilized as conductors of blood to and from the transplant. The kidney and adrenal were transplanted in mass, the renal artery being anastomosed to the carotid, the renal vein to the external jugular vein, and the kidney was removed at a later date. These procedures were carried out on seven dogs which have

remained in good condition for a number of months with a single adrenal that was located beneath the skin of the neck

The animals with a single transplanted adrenal maintain their weights, play and fight as do normal dogs. One became pregnant and gave birth to a normal puppy. Evidence that the transplant begins to function at an early date is found in the one experiment in which the right adrenal was removed 13 days prior to transplanting the left one. Evidence that the transplant will live when the second adrenal has not been removed is suggested by experiments in which transplantation of the left adrenal preceded the removal of the right one by one month. The arteriovenous difference in oxygen of the transplant is exceedingly small. Tests for epinephrine were made and in no experiment was there an unequivocal inhibition of the intestinal strip by venous blood from the transplant. The survival period of the one animal in which the transplant was removed for determining this point was slightly less than five days. The four transplants, which have been removed and examined, appeared normal grossly. On microscopic study the cortex and medulla and the ganglia surrounding the adrenal were found to be essentially normal. Only unmyelinated fibers were present in the transplanted adrenal. Material removed at autopsy from the region of the usual location of the glands did not reveal accessory adrenal tissue.

It is a pleasure to express our thanks to Dr. Barney Brooks and to Dr. Sam L. Clark.

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# RENAL CARBUNCLE

## CASE REPORT AND COMPARATIVE REVIEW

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THE more widespread interest and recognition in cases of carbuncle of the kidney is demonstrated by an increasing number of communications on the subject in recent years. Whereas Graves and Parkins<sup>1</sup> found 66 cases in the 27-year interval, ending 1932, we have been able to collect 35 cases from the literature plus a personal case in the five-year period ending 1937.

Comprehensive descriptions of the disease have been well given by Brady,<sup>2</sup> O'Connor,<sup>3</sup> Moore,<sup>4</sup> and others. In brief, a renal carbuncle may be defined as a circumscribed, multilocular, suppurative process in the renal parenchyma, metastatic in origin and usually caused by the *Staphylococcus aureus*. The striking similarity of its gross appearance to a carbuncle of the skin and subcutaneous tissues was first commented upon by Israel,<sup>5</sup> in 1905.

Graves and Parkins point out that the chief interest in this entity lies in its relative rarity and the difficulties attendant upon its diagnosis. In their series, urography played a minor part in the diagnosis, and nephrectomy was the most commonly employed therapeutic measure. On the other hand, in the case herewith reported, the definite aid furnished by intravenous pyelography and the satisfactory outcome of a conservative operation for an extensive lesion have been so gratifying, that we have been prompted to analyze the cases reported since the review of Graves and Parkins, with particular reference to earlier diagnosis, the rôle of urography, and the status of conservative surgery. We shall first report our case and then present the data obtained from a study of the last 36 cases recorded, making certain comparisons with the conclusions of the previous reports.

**Case Report**—(Referred by Dr. L. E. Clark) B. P., white, male, age 13, was admitted to the Dallas Medical and Surgical Clinic, June 15, 1937, complaining of pain in right flank, and fever. The patient had always been healthy and athletic. Six weeks previous he had developed measles. After the usual course of this disease, he felt quite well and was up and about until one month ago, when he began to have pain in the right side of the abdomen, epigastric distress and fever, which had continued to the time of admission. For the past three weeks he had been confined to bed. The temperature would rise to 102° to 104° F. each afternoon. He had had two rigors. At no time had there been any frequency, urgency, hematuria or dysuria. Numerous urinalyses had been normal. His appetite had been poor and he had lost 12 pounds in weight. Aside from

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the measles he had had no recent infections, colds, boils, or other septic foci. At times there had been considerable pain in the right lower chest on deep breathing, suggesting pleurisy.

*Past History*—Always in good health. Had had measles, mumps, pertussis, chicken-pox, pneumonia, and typhoid fever. His family history was irrelevant.

*Physical Examination*—Essentially negative except for the abdomen, which was flat and tender on the right side. On deep inspiration, a smooth, tender, indefinite mass could be felt below costal margin on the right, which did not feel like liver. Temperature 101° F, pulse 120, respiration 22.

*Laboratory Data*—Urinalysis: Straw-colored, cloudy, specific gravity 1.014, alkaline, no albumin, no sugar, sediment—negative. Blood examination: Hemoglobin 75 per cent, red blood cells 3,840,000, white blood cells 13,500, polymorphonuclear leukocytes 85 per cent, lymphocytes 12 per cent, large mononuclears 3 per cent. Kahn test negative. No malarial parasites found. Widal B *typhosus* agglutination in dilution 1:20 and 1:40. Para A and Para B—no agglutination.

*Roentgenologic Examination*—June 24, 1937. The outline of the left kidney is fairly well seen and is apparently normal. The right kidney outline cannot be definitely made



FIG 1—Intravenous pyelogram showing obliteration of the middle calyx of the right kidney.

FIG 2—More detailed roentgenogram of the right kidney pelvis.

out. The spine is normal. Psoas muscle shadows are visualized. An intravenous pyelogram shows the dye appearing rapidly on the left side, slowly on the right. The pelvis and calices are normal on the left. On the right, there is a filling defect in the region of the middle calyx completely obliterating it and indenting the pelvis. The outer margin of the right kidney is indistinct but apparently the organ is enlarged (Figs 1 and 2). Roentgenograms of the chest are essentially negative. *Preoperative Diagnosis*: Carbuncle of right kidney.

*Operation*—June 25, 1937. Dr. Harry M. Spence. Under gas-ether anesthesia, a five-inch incision was made parallel to and just below the last right rib. The perirenal tissues were indurated and edematous, and the fat friable. The mass involving the kidney was freed by blunt dissection. The kidney was freed from the inflammatory perirenal tissues with difficulty and delivered. Both upper and lower poles were essentially normal. The middle of the kidney was occupied by a typical, honeycombed, carbuncular lesion approximately two inches in diameter. Its surface was raised and showed numerous necrotic foci. Some thick greenish-yellow pus was oozing out in places. The true capsule was stripped from the kidney throughout its extent, a portion of the carbuncle was then enucleated and the remainder was drained by criss-cross incisions. A gauze wick was placed in the resultant cavity. Two empty rubber wicks were inserted to the upper and lower poles of the kidney.

*Pathologic Report*—Culture of pus from the lesion showed a heavy growth of

*Staphylococcus aureus* and a few colonies of nonhemolytic *Streptococci*. The gross specimen consists of a piece of irregular, friable, fibrin-coated tissue 3x2x1 cm. On section, it contains intercommunicating small abscess cavities with intervening necrotic tissue. Microscopically, there is diffuse infiltration with leukocytes, and little recognizable renal tissue. *Pathologic Diagnosis*: Carbuncle of right kidney.

*Subsequent Course*—The patient did well postoperatively. During the first day the temperature rose to 101.4° F but subsequently never went above 100° F. One drain was removed on the tenth postoperative day, and the others shortly after. There was copious drainage for about two weeks, but it gradually diminished and at the end of a month the wound was well healed. There was a rapid gain in weight and strength.

*Follow-Up*—Three months after operation, the patient appeared healthy and had no symptoms. The wound was solid. Urinalysis negative. Several reports by letter state that his health continues perfect.

*General Statistical Analysis*—The 66 cases, reviewed by Graves and Parkins, with our subsequent 36, make a total of 102 reported to date. Although Brady,<sup>2</sup> in 1935, reported on 105 cases, we have chosen the former survey as better adapted for comparison with our more recent series. Several cases, in which the diagnosis was questionable<sup>6</sup> or the information available too meager,<sup>7</sup> have not been included. In Table I, the salient features of the cases studied have been summarized.

Of the 36 cases, there were 20 males and 16 females. The average age was 32, the youngest being 9 and the oldest 65. The right side was involved in 19 instances, the left in 16, one case had bilateral involvement. The two consistent, and often the only symptoms were chills and fever and pain in the renal area. All but one patient had pain in the involved side, 36 per cent had chills, and 60 per cent had fever. Unexplained weakness, malaise, loss of weight and strength, while variable, were often present. History or evidence of a primary focus of infection was elicited in 78 per cent and absent in 22 per cent. These foci included 11 boils, five carbuncles, five superficial abscesses, one paronychia, and a miscellaneous group consisting of mastitis, measles, blow on the flank, rheumatic endocarditis, badly diseased teeth, and a severe upper respiratory infection. There was an average interval of five and one-half weeks between the occurrence of the primary infection and the onset of symptoms referable to the carbuncle, and an additional average of 45 days elapsed before treatment was instituted for the kidney lesion. This latter figure represents a significant reduction of 16 days over the corresponding interval of time in the cases tabulated by Graves and Parkins.

*Physical Examination*—In every instance in which the records were complete, there was tenderness, graded from slight to marked, over the involved side. The presence of a palpable mass could be demonstrated in exactly half of the cases. Save for the general appearance of acute or chronic sepsis there were no other evident physical findings.

*Laboratory Data*—Analysis of the bladder urine was essentially negative in 25 of the 36 cases. A significant amount of pyuria was present in six instances, pyuria and gross hematuria in two instances, and no information given in three cases. The bladder or kidney urine was examined bacterio-

TABLE I  
ANALYSIS OF 36 CASES OF CARBUNCLE OF THE KIDNEY  
Roentgenologic Findings

Case No	Author	Probable Source of Infection	Preoperative Diagnosis	Psoas Shadow	Enlarged Kidney Outline	Distortion of Pelvis or Calices	Operation	Result
1	Kahle and Beacham	Boil on thorax	Cortical abscess of kidney	Not given	No	Present	Nephrectomy	Recovery
2	Kahle and Beacham	Carbuncle on buttock	(1) Perinephritic abscess (2) Cortical abscess of kidney	Obscured	Yes	No pyelogram	Enucleation and drainage	Death from pneumonia
3	Taylor	No infection on flank	Renal neoplasm	Not given	No	Present	Nephrectomy	Recovery
4	James	None	Carbuncle of kidney	Not given	No	Present	Nephrectomy	Recovery
5	Swartz	Carbuncle on neck	Not given	Not given	No	Present	Excision and drainage	Recovery
6	Swartz	Boils on forearm	Carbuncle of kidney	Not given	No	Present	Excision, drainage and nephrostomy	Recovery
7	Lazarus	Abscess of palm	Renal carbuncle	Indistinct	No	No	Incision and drainage	Recovery
8	Lazarus	Numerous boils Carbuncle of hip	Renal carbuncle	Indistinct	Yes	No	Incision and drainage	Recovery
9	Lazarus	None	Renal carbuncle	Obliterated	No	Present	Incision and drainage	Recovery
10	Lazarus	Boil on right elbow	Renal carbuncle	Obliterated	No	Present	Incision and drainage	Recovery
11	Lazarus	Boils	Renal carbuncle	Obliterated	Yes	Present	Excision and drainage	Recovery
12	Lazarus	Boil on buttock	Renal carbuncle	Obliterated	Yes	No	Incision and drainage	Recovery
13	Ercole	Furunculosis	Perinephritic abscess	Not given	No	Present	(1) Incision and drainage of perinephritic abscess (2) Nephrectomy—3 weeks later	Recovery

# RENAL CARBUNCLE

14	Gardini	Furuncle on knee	Not given	No	No	No pyelogram	Nephrectomy	Recovery
15	Kanbe, Sakuno and Okada	Abscess on toe	Renal carbuncle	Not given	Not given	Not given	Not given	Death due to cere- bral ab- scess
16	Szacsavay	Furuncle on thigh	Carbuncle of kidney	Not given	No	Present	Incision and drainage	Recovery
17	Peterson	Acute upper respira- tory infection	Not given	Not given	Not given	Not given	Nephrectomy	Recovery
18	Ball	None	Not given	Normal	No	Present	Nephrectomy	Recovery
19	Gusznick	Maxillitis, left	Cortical abscess of kidney	Not given	No	Present	Decapsulation and drainage	Recovery
20	Brady	Carbuncle of neck	Perinephritic abscess	Not given	Yes	No	Incision and drain- age	Recovery
21	Filippi	None	Carbuncle of kidney	Not given	Yes	No pyelogram	Nephrectomy	Recovery
22	McNulty	Not given	Not given	Not given	No	Present	Nephrectomy	Recovery
23	Woodruff and Grossman	Badly diseased teeth?	Carbuncle of kidney	Obliterated	Yes	Present	Nephrectomy	Recovery
24	Davidson	Rheumatic fever	(1) Carbuncle of kidney	Not given	Yes	Present	Incision and drainage	Recovery
25	Houtappel	Paronychia	(2) Wilm's tumor	Absent	No	Present	Nephrectomy	Recovery
26	Serebrennikov	Furuncle on thigh	Carbuncle of kidney	Not given	Not given	Not given	Nephrectomy	Recovery
27	Altshteyn	None	Tumor of kidney	Not given	Yes	Present	Nephrectomy	Death from dissem- inated tubercu- losis
28	Emmett and Priestley	None	Tumor of kidney	Indistinct	Yes	Present	Nephrectomy	Recovery
29	Bangerter	Upper respiratory infection	(1) Perinephritic abscess	Not given	Yes	Present	Nephrectomy	Recovery
30	Pedroso and Michm	Carbuncle on leg	(2) Carbuncle of kidney Renal carbuncle	Not given	Yes	Present	Nephrectomy	Recovery



TABLE I—Continued

Case No.	Author	Probable Source of Infection	Preoperative Diagnosis	Roentgenologic Findings			Operation	Result
				Psoas Shadow	Enlarged Kidney Outline	Distortion of Pelvis or Calices		
31	Maxwell	Staphylococcal skin lesion	(1) Perinephritic abscess (2) Carbuncle of kidney	Not given	Not given	Present	Nephrectomy	Recovery
32	Maxwell	Staphylococcal skin lesion	Perinephritic abscess	Not given	Not given	Present	(1) Incision and drainage of perinephritic abscess (2) Nephrectomy, later	Recovery Recovery
33	Droschl	Abscess of forearm	Renal carbuncle	Not given	Not given	No	Nephrectomy	Recovery
34	Hjort	Axillary abscess	Renal carbuncle	Not given	Yes	No Pyelogram	Enucleation and drainage	Recovery
35	Hencz	None	Nephroptosis	Not given	Yes	No	(1) Electrocoagulation of carbuncle, decapsulation and drainage (2) Nephrectomy, later	Recovery Recovery
36	Spence and Johnston	Measles ?	Carbuncle of kidney	Indistinct	Yes	Present	Enucleation and drainage	Recovery

logically in 21 cases, and found to contain no organisms on culture or smear, or both, in 11 instances. Six urine cultures were positive for *Staphylococcus*, two for *B. coli*, and two smears showed miscellaneous organisms. Contrary to the experience of some with coccal infections, in no case was the direct smear positive where the culture was negative. It is thus seen that in one-half to two-thirds of the cases, complete examination of the urine reflects no evidence of the pathologic process in the kidney. This is evidently due to the fact that the inflammatory area does not communicate with the pelvis.

Blood cultures were made in 11 cases, nine of which were negative. One was positive for *Staphylococcus hemolyticus* before operation and negative after, and one was positive for *Staphylococcus albus* after operation and negative before. Both of these cases recovered. The average white blood cell count was 17,400 in the 20 cases in which it was recorded, the maximum count was 28,600, the minimum 9,400. In only two cases was it under 10,000.

Results of culture or smear of pus obtained from the carbuncle at operation were recorded in 28 cases. In 27 of these, some strain of *Staphylococcus* was either present in pure culture or predominated. The organisms found were

<i>Staph aureus</i>	16 cases
<i>Staph aureus hemolyticus</i>	3 cases
" <i>Staph</i> "	3 cases
<i>Staph albus</i>	3 cases
<i>Staph aureus hemolyticus</i> + <i>B. coli</i>	1 case
<i>Staph aureus</i> + nonhemolytic <i>Streptococci</i>	1 case
"Gram-negative bacteria"	1 case

*Cystoscopic Examinations*—These examinations were not performed, or the results not given, in 13 cases. Of the 23 cystoscopies made, 13 were negative, and 10 showed pus or bacteria in the kidney specimen. Renal function was normal on the affected side in 14 cases, diminished in 7, and not given in 15.

*Diagnoses*—A correct preoperative diagnosis of renal carbuncle was made 21 times. The diagnoses in the remainder were: Perinephric abscess, 6, renal neoplasm, 3, nephroptosis, 1, and not given in 5. In one instance, carbuncle, neoplasm and tuberculosis were discovered in the same kidney.

*Roentgenologic Data*—The urographic methods utilized in diagnosis were as follows:

Intravenous pyelography	11 cases
Retrograde pyelography	10 cases
Both intravenous and retrograde pyelography	2 cases
Pyelography, method not stated	3 cases
Genito-urinary tract film only	4 cases
Total	30 cases

The urographic findings in these 30 cases were

Filling defect or deformity of the renal pelvis	16 cases
Enlarged kidney outline	15 cases
Absent or indistinct psoas shadow	10 cases
Obliteration of one or more calices	7 cases
Significant dilatation of renal pelvis	3 cases
Normal pyelograms	4 cases

In regard to the roentgenographic data, our series differs markedly from that of Graves and Parkins. Out of 66 cases, they found only 15 abnormal pyelograms, while out of 36 cases we noted 22 abnormal pyelograms, and in only four instances were normal pyelograms obtained. The only case in which they found the intravenous method had been employed was their own. While it is true that there is no single roentgenologic finding pathognomonic of renal carbuncle, the occurrence of caliceal obliteration or distorted pelvis, coupled with a suggestive history and physical examination, makes an otherwise tentative diagnosis definite, and warrants earlier surgical intervention. In 11 of the 21 cases correctly diagnosed before operation, the pyelogram was the chief criterion upon which the diagnosis was predicated, while in numerous others it offered evidence corroborative of the history and physical signs.

Fixation or elevation of the diaphragm on fluoroscopy or in the chest film was noted on several occasions. The sign of Mathé,<sup>8</sup> i. e. loss of mobility between the Trendelenburg and upright positions, was not looked for as often as its probable value would warrant.

*Treatment*—The treatment of this condition is obviously surgical. The type of operation to be performed, whether nephrectomy, incision and drainage, or enucleation of the carbuncle, depends upon the general condition of the patient and the degree of destruction of the kidney.

On reviewing the treatment in this series, we gain the distinct impression that as a general rule, unless more than a third of the kidney is involved, a conservative procedure seems preferable as the first step, and is more often than not sufficient by itself. This favorable outcome, however, presupposes thorough exploration, mobilization and adequate drainage of the lesion, usually including decapsulation. Drainage of the associated perinephric abscess alone was ineffective in clearing up the carbuncle or relieving the body of the burden of sepsis on several occasions.

It is important to consider the relationship of perinephric abscess to carbuncle of the kidney. From clinical observation, it seems likely that most perinephric abscesses result by extension from small, shallow, isolated cortical lesions which heal spontaneously after the abscess proper is evacuated. Carbuncle, while always accompanied by phlegmon of the surrounding tissues, seems to result in frank perirenal suppuration only in the later stages. In our group, perinephritis was found in all operated cases and perinephric abscess in 10, an incidence of 28 per cent. Unexplained prolonged drainage from a perinephric abscess should make one consider the possibility of renal carbuncle as the underlying cause.

Thirty-five patients were operated upon in this group of 36, the exception being a case dying of cerebral abscess and coming to autopsy. A primary

nephrectomy was carried out 17 times, with one death possibly from disseminated miliary tuberculosis three months after operation. Incision and drainage of the carbuncle was performed in nine cases with no fatalities. Partial or complete excision or enucleation of the lesion was performed in six cases, with one death from lobar pneumonia. In one of these cases a nephrostomy was performed when a calix was broken into. Two patients had a drainage of a perinephric abscess without recognition of the presence of a carbuncle, they failed to improve, and later secondary nephrectomy was performed. In one case the carbuncle was treated by electrocoagulation, but later required nephrectomy. In all, 52 per cent of these cases were originally treated by conservative operation.

The analysis of Graves and Parkins showed that in 63 operated cases nephrectomy was performed 39 times with seven deaths, a mortality of 17.9 per cent, incision and drainage was performed 19 times, with a mortality of 31.5 per cent, the carbuncle was enucleated in five cases with no deaths. When these figures are compared with those given above, namely, two deaths in 35 cases, or a mortality rate of 5.7 per cent, a marked improvement is evident. We ascribe this to earlier intervention, and the fact that conservative surgery was employed approximately twice as frequently in the more recent series.

The complications encountered, apart from the fatalities and prolonged wound drainage in several instances, were: Extension upward through diaphragm, Staphylococcus abscess of prostate requiring drainage, abscess at site of hypodermoclysis, multiple miliary cortical abscesses in opposite kidney, requiring decapsulation.

#### CONCLUSIONS

(1) Thirty-six recent cases of carbuncle of the kidney, including a personal case, have been analyzed and compared with a preceding series of 66 cases.

(2) An improvement of 16 days between the onset of symptoms and treatment of the carbuncle has resulted in the past five years.

(3) Urography is the greatest single objective aid in the diagnosis of renal carbuncle.

(4) Incision and drainage and enucleation are being employed more frequently with satisfactory results.

(5) The operative mortality in the last 36 cases has been only a third as great as in the first 66 cases.

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# THE EFFICACY OF "COLEY'S TOXIN" IN THE TREATMENT OF SARCOMA \*

AN EXPERIMENTAL STUDY

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SINCE the observations many years ago, that patients with sarcoma who accidentally contracted erysipelas sometimes exhibited regression of the neoplasm, attempts have been made to treat sarcomata by injection of bacterial products, particularly those of *Streptococcus erysipelatis* combined with *Bacillus prodigiosus*. Interest in laboratory research in this question has developed in the last few years and a number of publications have appeared indicating that certain bacterial products, especially those of meningococcus and *B coli*, were capable of inducing partial or complete liquefaction sometimes with complete regression of transplantable neoplasms in mice (and other animals). For a detailed review of the literature the reader is referred to the report of M J Shear<sup>3</sup> (1935).

There is some question as to the mechanism of such phenomena. According to some it is essentially an immunologic reaction of the nature of a Schartzman phenomenon. On the other hand, Shear and Andervont<sup>4</sup> have extracted from *B coli* filtrates a "hemorrhage producing fraction" whose action would appear to be a direct and specific one upon the capillaries of the tumor. Furthermore, Andervont<sup>1</sup> has indicated that the reactivity of a neoplasm to bacterial products depends to some extent upon the hereditary factors of the animal.

Among clinicians the late W B Coley<sup>2</sup> was the most enthusiastic proponent of the treatment of sarcoma, especially of bone, by bacterial products in man. For many years he advocated the use of killed suspensions of *Streptococcus erysipelatis* combined with *B prodigiosus* as an adjuvant to surgical and irradiation therapy. This mixture has become popularly known as "Coley's toxins". While the evaluation of the efficacy of the toxins alone under such conditions is difficult, a review of the accumulated case reports in the literature leaves an impression that one cannot conclude, at present at least, that the use of toxins was totally ineffective in all cases.

The purpose of the experiments recorded below was to study the effect of "Coley's toxins" (Parke Davis & Co.) and other bacterial products upon sarcomata in rats induced from the animals' own tissues as a result of subcutaneous injection in the interscapular region of a suspension of benzpyrene.

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or methylcholanthrene (2 to 3 mg per animal) in lard Sarcomata began to appear after four and one-half months following injection The animals employed were of unknown genetic history, the colony was derived from the Wistar strain coupled with those obtained from a local dealer

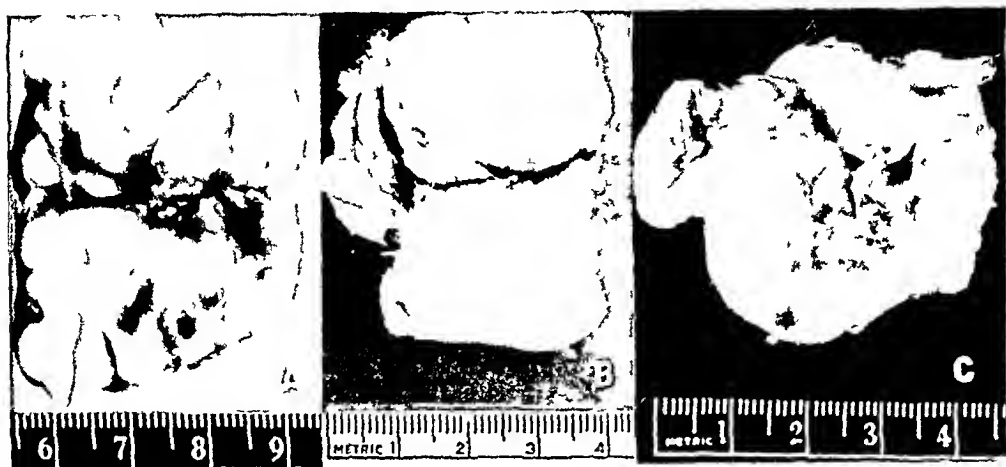


FIG 1—Compare with Fig 2 (A) Sarcoma from a rat receiving intraperitoneal injections of Coley's toxins but exhibiting no reaction there are a few small areas of spontaneous hemorrhage and necrosis (B) Sarcoma from an animal injected as in (A) showing firm, dense whitish tissue also no reaction (C) Sarcoma from a control rat that received no injections Partially collapsed central cavity was filled by orange red fluid, there is also spontaneous necrosis of the central portion of the tumor

**Control Observations**—Prior to evaluation of the effects of the bacterial products, control observations were made in a series of benzpyrene sarcomata to determine their natural course, especially as to the incidence and magnitude

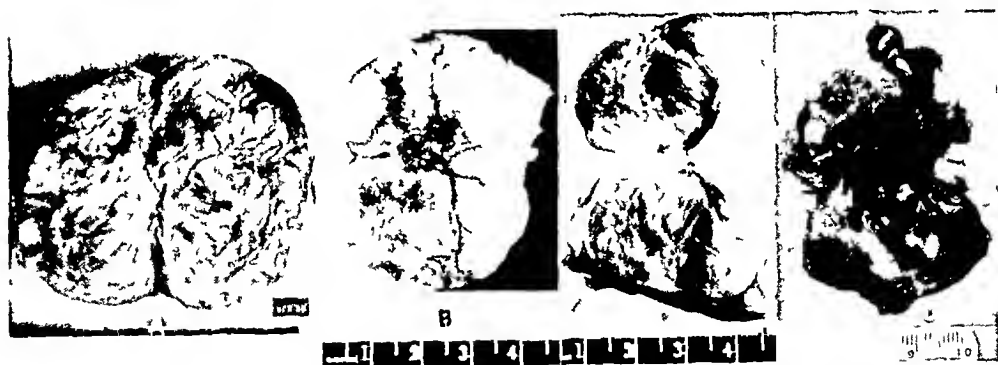


FIG 2—(A) Relatively mild diffuse hyperemia in a sarcoma from an animal injected with 2 cc of Coley's toxins 24 hrs previously. Animal died spontaneously (B) Moderately severe hyperemic reaction in a sarcoma from an animal injected 2 days previously with 2 cc of killed 7 day dextrose broth cultures of *Streptococcus erysipelas*. Note absence of reaction throughout a large portion of the tumor (C) Moderately severe hyperemic reaction throughout a tumor from an animal injected with 6.5 cc of Coley's toxins during 21 days and killed 22 days after the first injection. There was no apparent growth restraint (D) Intense hemorrhagic reaction in the tumor from an animal injected 24 hrs previously with 1 cc of Coley's toxins. Animal died spontaneously

of spontaneous hemorrhages and necrosis In 15 animals, specifically set aside for these observations from the larger group employed in the following experiments, it was found that the consistency of the tumors themselves varied from very hard, even suggesting the presence of bone, to a soft cystic con-

sistency denoting spontaneous liquefaction. The animals were killed at varying periods up to 60 days following daily palpation of the tumor, once it had become 1 cm or larger in diameter. In 12 cases the surfaces of the tumors appeared grayish and semitranslucent. On cut surface, *small* scattered areas of recent or old hemorrhage were often seen and in some tumors large, central yellowish areas of necrosis were present. In two instances large blebs of reddish-orange fluid were present, once within the tumor and once beneath the "capsule." These blebs composed a large part of the gross bulk of the neoplasms and gave it a cystic quality on palpation *in vivo*. Adjacent to, or surrounding the blebs, the tumor tissue was reddish-yellow, necrotic and amorphous. In another instance the entire tumor, measuring 5 by 3 cm, became cystic while under observation, and at necropsy was found to be composed of semisolid, reddish-orange, amorphous material resembling a clot in consistency but not in color.

In the series reviewed above, and in a number of other rats bearing similar tumors and employed in other experiments, it was observed that the natural rate of growth in these neoplasms varied widely. Some grew only several millimeters in diameter over a period of three to four weeks while others grew to 10 cm in diameter over a similar period.

In none of the animals observed in the appended experiments was there evidence that intraperitoneal injections of the bacterial products resulted in growth restraint of the sarcomata, on the other hand, some effects were noted.

When the animals died or were killed and the tumors excised and bisected the following criteria were employed to record results:

(1) Grayish or yellowish-gray tumors were regarded as exhibiting no effects due to bacterial injections.

(2) Large yellowish areas of central necrosis were regarded as spontaneous changes.

(3) Areas of liquefaction, where the fluid and surrounding tumor tissue exhibited an *orange-red color*, were regarded as spontaneous changes since they had been observed in the control series described above.

(4) Diffuse hyperemia (red or dark red color) with or without areas of softening, the latter when present resembling a blood clot and distinctly different from the areas of liquefaction observed in (3) were regarded as effects due to injection of bacterial products since in no instance in the above control or in other experiments were such changes observed to occur spontaneously.

Experiment 1—Intraperitoneal injection of Coley's toxins in rats bearing benzpyrene sarcomata. This product proved to be quite toxic for the animals in the doses administered, since of a total of 22 animals 10 died within 48 hours after receiving one injection of 1 to 2 cc.

Of the latter, four tumors showed positive effects, six were negative.

Of the remaining 12, Coley's toxins in doses of 1 to 2 cc were administered every 24 to 48 hours to total doses of 6 to 14 cc over periods varying up to 25 days. The animals were killed at intervals of 4 to 30 days following the first injection. Of this series three showed positive effects and nine were negative.

Experiment 2—Intraperitoneal injection of killed (heating to 56° C for 12 hours) 7 day dextrose broth cultures of *Streptococcus erysipaelis* obtained from the stock of the Department of Bacteriology of the University of Chicago. In 15 animals exhibiting benzpyrene sarcomata, doses of 3 to 5 cc were injected at intervals of one to two days. This preparation was not as toxic as the product used in Experiment 1. The animals were killed 1½ to 78 days following total doses of 3 to 16 cc. Of the 15 tumors two exhibited positive reactions.

Experiment 3—Intraperitoneal injections of killed 7 day dextrose broth cultures of a hemo-



lytic strain of *B. coli*. In eight tumor bearing animals 5 cc doses were injected every one to two days. Two animals died after one injection, in one of them the tumor exhibited a positive reaction. Six animals were permitted to survive 14 to 27 days receiving total doses of 14 to 26 cc. In two of the latter series the tumor exhibited a positive reaction and four were negative.

Experiment 4.—Intraperitoneal injection of killed 7 day broth cultures of *B. prodigiosus*. The latter strain was obtained from the stock cultures of the Department of Bacteriology. Seven tumor bearing rats received daily doses of 2, 3, 4 and 4 cc respectively for four days. One died six days after the first injection. The tumor exhibited a positive reaction. The remaining six animals were observed for 28 days and when killed all the tumors were negative. At no time during the period of observation did any of the tumors exhibit softening.

Experiment 5.—Control experiments were conducted upon eight tumor bearing rats to show that doses of previously heated (56°C) sterile dextrose broth equivalent in volume to the bacterial suspensions used above would not induce hemorrhagic reactions in the tumor.

Experiment 6.—Onset of acute chemical inflammation were induced by the subcutaneous injections of 0.2 cc of croton oil in 12 rats. Forty eight hours later 2 cc of Coley's toxins were injected intraperitoneally in six animals. All animals were killed three to five days later. The acute inflammatory reactions were approximately of equal intensity in the control and injected rats.

*Histologic Study*.—A histologic study of the tumors which grossly exhibited hyperemia and hemorrhagic necrosis as a result of injection of bacterial products showed essentially the same picture exhibited in the small foci of spontaneous necrosis or spontaneous hemorrhage in control tumors or such areas in tumors not affected by these products, i.e., widely dilated capillaries, interstitial exudate of red blood cells, local polymorphonuclear infiltration, shrunken appearance of the tumor cells, etc. The tumors produced in the above animals exhibited varying histologic pictures and consisted of large spindle cell, small spindle cell or "pleomorphic cell" sarcomata. No correlation was possible between the histologic type of the tumor and its positive or negative response to intraperitoneal injections of bacterial suspensions. In none of the animals was there macroscopic evidence of lesions in other organs or tissues that might have been ascribed to the injected materials.

*Discussion*.—In the foregoing observations no evidence was obtained to indicate that Coley's toxins, or the other bacterial suspensions, inhibited the growth of sarcomata induced from the animals' own tissues by carcinogenic hydrocarbons. The acute hyperemia and hemorrhagic exudations that did occur, presumably due to such injections, did not result in appreciable growth restraint. As far as can be determined, the only other observations of this type reported upon sarcomata induced from the animals' own tissues by hydrocarbons are those of Andervont. This investigator found that *B. coli* filtrates "produced hemorrhage with regularity in primary 1, 2, 5, 6 dibenzanthracene tumors," but that "thus far, complete recession of primary dibenzanthracene sarcomata has not occurred."

The mechanism of the "hemorrhagic reaction" observed in some of the cases remains obscure. The assumption that it is an "immunologic phenomenon" also necessitates the assumption that the tumor tissue was primarily hypersensitive to certain bacterial products, a fact not yet demonstrated. The work of Shear and Andervont in obtaining a fraction from *B. coli* filtrates which exhibited a high potency as regards hemorrhage production in transplantable tumors would suggest that bacteria elaborate, in some form or another, a substance highly specific for the vascular system of tumors. Experiment VI was performed to observe whether in an acute inflammatory focus the capillaries are in a hypersensitive state in regard to bacterial products. It was felt that a tumor presenting in a substantial part of its mass inflammatory reaction due to spontaneous necroses might thus prove to be hypersensitive to

bacterial products The results of this experiment, however, were negative Furthermore, in the observations made above it would appear that the hyperemic and hemorrhagic reaction when once inducted are not ephemeral phenomena but persist for some time

#### SUMMARY

(1) The effects of intraperitoneal injections of "Coley's toxins," of killed 7-day dextrose broth cultures of *Streptococcus dysipelatis*, of killed 7-day dextrose broth cultures *B prodigiosus*, and of killed 7-day broth cultures of *B coli* were studied upon sarcomata of the subcutaneous tissues of rats, induced from the animals' own tissues by carcinogenic hydrocarbons Transplanted neoplasms were not employed

(2) No evidence of inhibition of growth of the tumors was obtained

(3) In a significant number of instances the tumors of injected animals exhibited a marked hyperemic and hemorrhagic reaction It is assumed that this was a reaction to the injection of bacterial products since such changes were not observed in control animals, and were definitely of a different type, macroscopically, than the spontaneous degenerative changes sometimes observed in such neoplasms These reactions, as indicated, did not appear to markedly restrain the growth of the neoplasm

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# MULTIPLE DENTIGEROUS CYSTS\*

WITH SPECIAL REFERENCE TO OCCURRENCE IN SIBLINGS

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CERTAIN tumors and cysts occur in the jaw bones which depend for their origin upon abnormal growth of epithelial cells connected with the enamel organ of the tooth. In order to better understand their development, attention is called to certain pertinent embryologic facts. The earliest indication of the formation of the tooth germ is the down-growth of epithelium from the mouth surface at about two and one-half months of embryonic life—the dental lamina. The undersurface of this bud-like down-growth becomes indented by the connective tissue of the dental papilla, from which the mesoblastic parts of the tooth are formed. The epithelium then encapsulates the dental papilla to form the enamel organ in two layers—the outer and inner layers of the enamel organ. Between the two layers is a mass of stellate cells in a mucoid substance—the stellate reticulum or enamel pulp. The cells of the inner layer of the enamel organ become the ameloblasts, which build enamel. This layer of cells is prolonged downward and surrounds the connective tissue from which eventually the dentine and cementum of the tooth are formed. This downward prolongation of epithelium is called the sheath of Hertwig. The outer connective tissue cells of the dental papilla become the odontoblasts, by which dentine is formed. Some of the epithelial cells of the sheath of Hertwig persist in the mature dental periosteum surrounding the root of the tooth as small isolated groups, which are known as the paradental debris or epithelial cell-rests of Malassez. The outer epithelial layer of the enamel organ lies in contact with the connective tissue surrounding the unerupted tooth germ and eventually becomes the so-called Nasmyth's membrane, disappearing after the tooth erupts. The different forms of tumors and cysts of dental origin can be explained by abnormal growth of certain portions of the developmental epithelium above described.

There are three main types of pathologic growths arising from the dental epithelium.

(1) The *adamantinoma* or *ameloblastoma*, which may be said to take its derivation from the entire enamel organ, and histologically presents a structure representing different parts of this organ, namely, cells resembling the ameloblasts, the stellate reticulum, etc.

(2) The *dental root cyst*, or *radicular cyst*, almost always a sequela of chronic inflammation about the apex of a tooth as a result of infection following death of the dental pulp. The epithelial lining of the cyst is believed by

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most writers to be derived from the paradental epithelial cell-rests of Malassez, which are remnants of the cells of the enamel organ persisting in the adult dental periosteum

(3) The *dentigerous* or *follicular cyst*, to a consideration of which the present paper will be limited. The dentigerous cyst takes its name from the fact that it *bears a tooth* and forms a hollow swelling in the bone, usually filled with straw-colored fluid and having a partially or fully developed tooth attached by its root to the wall of the cyst, with the crown projecting into the cavity. There is a lining membrane, the inner portion consisting of several layers of squamous epithelium, believed to be derived from the outer layer of epithelium of the enamel organ. These cysts are usually first noticed about the period of eruption, nearly always in connection with the permanent teeth. Any tooth may be involved, most commonly the canine and the third molar, or a supernumerary tooth may be the origin of the cyst. Teeth of the upper and lower jaws are about equally involved. From the foregoing, it is evident that the term dentigerous should not be applied indiscriminately to all cysts of dental origin, as is occasionally noticed in the literature,<sup>6 13</sup> but only to those having the crown of an unerupted tooth in the cavity.

*Etiology and Pathogenesis of Dentigerous Cysts*—The cause of these anomalies has given rise to considerable speculation. The most reasonable theory appears to be that the cyst is the result of accumulation of fluid between the inner and outer layers of the enamel organ, at the expense of the stellate reticulum. The sac gradually enlarges, expanding the surrounding bone, the outer layer of the enamel organ epithelium persisting as the lining membrane. The crown of the tooth involved projects into the cyst cavity, with the lining membrane attached to its neck. Just what starts the process is not known. Bloch-Jørgensen<sup>2</sup> disputes this conception. He states that "the follicular (*i e*, dentigerous) cyst is never formed from the permanent tooth germ, but is in fact a radicular cyst of the deciduous tooth, causing involvement and retention of the permanent tooth." Thoma<sup>18</sup> disagrees with this for several reasons, pointing out that dentigerous cysts may occur in connection with deciduous teeth and describes a case of this character, they also form in connection with permanent molars which are never in contact with infected deciduous teeth, and the most frequent site of a dentigerous cyst is the mandibular third molar. Thoma criticizes Bloch-Jørgensen's cases as not having the characteristic epithelial lining of cysts, and that their roentgenographic appearance is characteristic of osteitis.

Lartschneider<sup>11</sup> believes that the pathogenesis of dentigerous cysts is an inflammation of the dental follicle, either caused by local infectious processes of neighboring teeth, especially deciduous teeth, or by peritonsillar infections, stomatitis or gingival ulcerations, or by trauma. Thoma is of the opinion that Lartschneider's theory can be correlated better with the generally accepted conception of the development of dentigerous cysts than that of Bloch-Jørgensen. Sprawson<sup>16</sup> also suggests that "dentigerous cysts are all primarily dental (root) cysts, usually formed in connection with septic deciduous teeth

and in the same manner as that in which we believe the ordinary dental (root) cyst connected with a septic permanent tooth to be formed, that in their growth and extension in the direction of least resistance they meet with and surround an adjacent developing unerupted tooth gradually enveloping it—in this way eruption is prevented” These theories do not satisfactorily explain undoubted cases of dentigerous cysts where no sepsis of deciduous teeth exists, or dentigerous cysts connected with unerupted third molar teeth which develop in regions of the jaw far removed from deciduous teeth Latschneider attributes these latter to tonsillar infection, but it seems rather far-fetched to suppose that tonsillar infection could reach the tooth follicle without any evidence of osteitis in the intervening bone So far, no satisfactory etiologic theory has been advanced to fit all cases

Jourdain,<sup>10</sup> in 1778, described three cases of cysts of the jaws connected with unerupted teeth From this time on, mention of dentigerous cysts occurs with increasing frequency in the literature<sup>3 5</sup> With the advent of roentgenologic diagnosis, the discovery of clinically unsuspected cases has become commonplace

*Clinical Course*—Dentigerous cysts begin before the time of normal eruption of permanent teeth Symptoms are absent at first, but suspicion may be aroused by absence of a permanent tooth when the normal time for its eruption has passed Later, as the cyst enlarges there is a painless, gradually increasing swelling of the jaw bone, at the site of the unerupted tooth, usually involving the outer plate especially As the bone thins out, the overlying gum bulges, and a characteristic parchment or celluloid-like feeling is noted Suppuration may occur, with inflammatory symptoms The swelling may become so large that it may be visible externally Roentgenologic examination shows a clear area of absence of bone, with well defined margins, with the crown of the unerupted tooth projecting into it In the upper jaw, the cyst may push up the floor of the maxillary sinus in a dome-like manner, encroaching on the space normally occupied by the latter, though seldom actually perforating into the sinus If permitted to continue untreated, a dentigerous cyst may extend around the roots of adjacent normal teeth, cutting off their blood supply and eventually causing loss of these teeth The bone may become so thinned out that slight trauma produces a pathologic fracture

*Multiple Dentigerous Cysts*—Instances of single dentigerous cysts are quite common, but it is unusual to find more than one such growth in the jaws of a single individual Instances of this occurrence, however, have been reported, and we have been able to find the following recorded in the literature It is probable that many others have occurred but have never been reported, and some references may have been overlooked

The earliest case of multiple dentigerous cysts would appear to be that recorded by Glaswald in 1844<sup>7</sup> The patient had two dentigerous cysts in the maxilla, one connected with the right canine and the other with the left first premolar, and was operated upon successfully by Baum Hern,<sup>9</sup> in 1894,

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recorded three such cysts in a boy, age 9, two in the maxilla and one in the mandible. Sprawson<sup>16</sup> found three in a boy, age 18, all in the lower jaw. Grellier's<sup>8</sup> patient was 13 years of age and both maxilla and mandible contained cysts. Limberg<sup>12</sup> reported the case of a woman, age 22, with dentigerous cysts connected with the four third molar teeth. He mentions a case of Reismöller<sup>12</sup> in which six dentigerous cysts were present.

Starup<sup>17</sup> reports two cases of multiple dentigerous cysts in the lower jaw. Bennett's<sup>1</sup> case presented cysts involving unerupted right maxillary and left canines and right third molar, right mandibular incisor and left third molar. Wigginton<sup>19</sup> published a report entitled Three Cases of Dental Cysts in One Family. The father, 30 years before, had a cyst removed from the right maxillary canine region, and five years before loculated cysts were removed from the right and left ramus of the mandible. The last two were almost certainly dentigerous. One son, age 11, had a dentigerous cyst involving the right mandibular canine, and the other son, age 9, a dentigerous cyst of the right mandibular third molar. Seeman's<sup>14</sup> case was a male, age 16, with four cysts involving unerupted maxillary and mandibular third molars. Shea<sup>15</sup> recently described a case, evidently of multiple dentigerous cysts, in which the upper jaw and maxillary sinus and the mandibular third molar region were involved (Table I).

TABLE I

TABULATION OF CASES OF MULTIPLE DENTIGEROUS CYSTS THAT HAVE BEEN RECORDED

Author	Sex	Age	Location of Cysts
Glaswald <sup>7</sup>	F	38	2 in maxilla
Hern <sup>9</sup>	M	9	2 in maxilla 1 in mandible
Sprawson <sup>16</sup>	M	18	3 in mandible
Grellier <sup>8</sup>	—	13	1 in maxilla 1 in mandible
Limberg <sup>12</sup>	F	22	2 in maxilla 2 in mandible
Reismöller <sup>12</sup>	—	—	6 cysts, location not specified
Starup <sup>17</sup>	—	—	2 in mandible
Starup <sup>17</sup>	—	—	2 in mandible
Bennett <sup>1</sup>	F	23	3 in maxilla 2 in mandible
Wigginton <sup>19</sup>	M	40?	2 in mandible
Seeman <sup>14</sup>	M	16	2 in maxilla 2 in mandible
Shea <sup>15</sup>	—	—	2 in maxilla 1 in mandible

*Prognosis*—Dentigerous cysts in their usual development are quite benign, and can readily be eradicated by suitable operation. Occasionally, however, the epithelial lining may take on an invasive character, so that, instead of a single cavity filled with fluid and an unerupted tooth, solid masses of the epithelial cells may extend from the wall of the cyst and even spread through the bone into the soft tissues. This aberrant growth of dentigerous cyst epithelium bears some resemblance to adamantinoma and has caused a diagnosis of the latter by pathologists not intimately familiar with the histologic picture. Some pathologists go so far as to state that dentigerous cysts can occasionally develop into adamantinoma. Churchill<sup>4</sup> has clearly pointed out the differences between the two. However, from the standpoint of prognosis, when the epithelium of a dentigerous cyst takes on this aberrant and invasive character, the chances for cure are not so good and recurrence is more to be feared following conservative operation than in the case of the usual unilocular dentigerous cyst. Dentigerous cysts remaining untreated may gradually spread and involve adjacent healthy teeth, may become infected, leading to osteomyelitis and cellulitis, in the upper jaw, may invade the maxillary sinus, and in the lower jaw the bone may become so thinned-out that a pathologic fracture results.

*Treatment*—In the ordinary dentigerous cyst a flap of gum is turned down over the bulging cyst wall, a sufficient amount of this is cut away with scissors, rongeur forceps or chisel to expose the cyst cavity. The epithelial lining is shelled out, and if the involved tooth is not in a position to erupt normally, or is deformed, it is removed. However, in many cases the tooth can be allowed to remain and may eventually erupt normally. In small dentigerous cysts after the lining and the unerupted tooth have been removed, especially in the upper jaw, the bone cavity can be allowed to fill with blood and the flap sutured over it. The clot frequently remains sterile, undergoes organization, and is eventually replaced with new bone. In larger cysts, the cavity is kept open with packing for a few days, and later treated by irrigation until it fills in with granulation. In the case of aberrant and invasive growth of the cyst lining, radical resection of the involved portion of the jaw may be necessary, just as in the case of adamantinoma.

To the foregoing cases of multiple dentigerous cysts found in the literature, the following cases that have come under personal observation are added, including three and possibly a fourth which occurred in children of the same family.

**Case 1**—N. H., female, age 14, was first seen October 19, 1928, and complained of chronic, painless enlargements of both sides of the lower jaw. She was a very large girl for her age, had been undergoing orthodontic treatment for two or three years previously, and it was noticed that certain teeth did not erupt at the normal time. This led to roentgenologic studies which revealed the following unerupted teeth: Right maxillary second premolar and third molar, left maxillary third molar, right mandibular third molar, and left second and third molars (Figs. 1 and 2). Five distinct cysts were associated with these unerupted teeth. The largest cyst was that connected with the left mandibular second and third molars, and it extended forward beneath the roots of the

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erupted teeth around the symphysis of the mandible to the right second premolar region. The root ends of some of the incisor teeth had become eroded by the cyst. Clinically, the cysts were more evident in the lower jaw than in the upper, and the bone was seen to be thinned out and expanded beneath the erupted teeth on each side.

*Operative Procedures*—October 26, 1928. The cysts in the lower jaw were opened through intra-oral incisions, the epithelial lining shelled out and the unerupted teeth removed.

June 21, 1929. The cysts on each side of the upper jaw were enucleated and the unerupted teeth removed. There were two distinct sacs on the right side and one on the left.

In January, 1932, at the age of 18, some swelling and discomfort were noticed in the left lower jaw at the site of the previously removed third molar. A probe could be passed through an opening in the gum into a cavity in the bone. Roentgenologic examina-

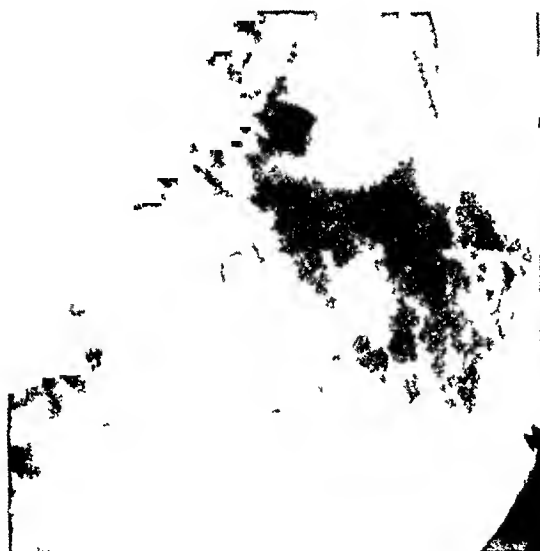


FIG 1—Case 1. Radiograph of right side, showing dentigerous cysts connected with maxillary second premolar and third molar, mandibular third molar.



FIG 2—Case 1. Radiograph of left side, showing dentigerous cysts connected with maxillary third molar and mandibular second and third molars.

tion showed a small, clear-cut cavity in this region, evidently a recurrence, due to incomplete removal of the cyst lining. The gum was incised and the lining of the bone cavity was shelled out; roentgenologic studies made a few months later showed obliteration of the cyst cavities by regeneration of bone.

In August, 1936, the patient, then age 22, returned with a discharging sinus over the upper left incisor region, and a probe was passed back into a large cavity containing pus and cheesy material. This did not communicate with the maxillary sinus. Roentgenologic examination revealed a large cystic cavity over the roots of the remaining upper left teeth, evidently a recurrence of the original cyst from the third molar, with secondary exposure of the roots of the teeth farther forward. There has been no further trouble since the removal of all remaining upper teeth on the left side and enucleation of the cyst lining. Roentgenologic studies have shown good bone regeneration in the regions formerly occupied by cysts. Careful studies have been made from time to time in this patient, owing to her peculiar growth and anatomic build, to determine the presence of a disturbed calcium metabolism or endocrine abnormality, without results.

**Case 2**—R. B., female, age 18, was first seen April 5, 1937. While in a nurses' training school in a Pittsburgh hospital, a routine roentgenologic examination of the teeth revealed several cystic areas in the upper and lower jaws, although she had complained of no symptoms. Examination showed the patient to be very tall, with the upper jaw somewhat underdeveloped as compared to the lower. Nothing else abnormal



was observed in the mouth except that certain teeth were missing. The cystic areas in the jaws were shown roentgenologically to be connected with the unerupted right maxillary third molar, right mandibular second molar, left mandibular second premolar and third molar teeth (Figs 3 and 4).



FIG 3—Case 2 Radiograph of right side showing dentigerous cysts connected with maxillary third molar and mandibular second molar



FIG 4—Case 2 Radiograph of left side, showing dentigerous cysts connected with mandibular second premolar and third molar

*Operation*—June 22, 1937. Four separate dentigerous cysts and the unerupted teeth were removed, through incisions in the gum. Recovery was uneventful.

*Case 3*—E. G., female, age 12, was first seen June 26, 1933 and gave the following history. About six months previously the right side of the face over the lower jaw began to enlarge, and had progressively increased in size, without any accompanying pain.



FIG 5—Case 3 Radiograph of right side showing dentigerous cysts connected with mandibular canine and third molar



FIG 6—Case 3 Radiograph of left side showing dentigerous cysts connected with mandibular second incisor, canine and second molar

One month before she was first seen, some deciduous teeth had been extracted from the left side of the mandible, and pus and blood had been draining from the gum ever since.

*Physical Examination* showed the right side of the lower part of the face to be visibly enlarged, and a bulging of the gum beneath the lower teeth on this side, with parchment-like crackling, was noted. On the left side there was an opening through the gum in the premolar region discharging pus, and a probe passed down into a cavity in

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the bone. Roentgenologic examination revealed a multiple cystic condition of the mandible involving the following unerupted teeth: Right mandibular canine and third molar, left second incisor, canine, and second molar (Figs 5 and 6).

*Operation*—June 27, 1933. Under ether anesthesia, flaps were made in the gum on both sides of the lower jaw and at least three distinct cysts were noted, containing clear fluid and pus. The lining of the cysts was shelled out and the five unerupted teeth were



FIG 7—Case 3. Radiograph of right side, showing bone regeneration several months after operation on dentigerous cysts.



FIG 8—Case 3. Radiograph of left side, showing bone regeneration several months after operation on dentigerous cysts.

removed. The cyst cavities passed high into the ascending ramus on the right side. In enucleation of the lining, the inferior dental nerve was exposed but left intact. The cavities were packed with gauze for a few days, and then treated by irrigation until healing occurred. Roentgenologic examination several months later showed regeneration of bone and obliteration of the cyst cavities (Figs 7 and 8).



FIG 9—Case 4. Radiograph showing dentigerous cyst connected with right maxillary canine.



FIG 10—Case 4. Radiograph showing dentigerous cyst connected with left maxillary canine.

**Case 4**—J. G., male, age 11 (brother of Case 3), was first seen December 6, 1937. He had had no symptoms, but it was noticed that certain teeth had not erupted at normal time. Roentgenologic examination revealed three distinct dentigerous cysts, connected with the maxillary canines and the right mandibular first premolar (Figs 9, 10 and 11).

It was suspected also that a fourth cyst was present in the right mandibular third molar region.

*Operation*—January 4, 1938 The cyst linings were enucleated and the unerupted teeth removed. The right mandibular third molar region was not disturbed, but will be studied roentgenologically again. Pathologic examination showed the cyst wall to



FIG 11—Case 4 Radiograph showing dentigerous cyst connected with right mandibular first premolar



FIG 12—Case 5 Radiograph showing dentigerous cysts connected with left mandibular canine and first premolar

be composed of squamous epithelium and fibrous tissue. The patient was discharged in good condition January 31, 1938.

*Case 5*—B G, female, age 10 (sister of Cases 3 and 4), was examined December 6, 1937, following the discovery of cysts and unerupted teeth roentgenologically. No symptoms were present. Roentgenologic examination showed two dentigerous cysts, connected with the unerupted left mandibular canine and first premolar (Fig 12).

*Operation*—January 4, 1938 The cyst cavities were exposed by turning down a flap of gum, and found to be filled with a clear fluid. The canine tooth lay at the bottom of the cavity near the lower border of the mandible. Both unerupted teeth were removed and the cyst linings shelled out. Pathologic examination showed a layer of squamous epithelium. The cavities gradually filled in by granulation and the patient was discharged January 31, 1938.



FIG 13—Case 6 Radiograph showing dentigerous cyst forming around crown of unerupted left mandibular first premolar

*Case 6*—G G, female, age 8 (youngest child in the same family as Cases 3, 4 and 5), was first seen in December, 1937. In view of the family history of dentigerous cysts, this child's jaws were also studied roentgenographically to determine whether she too had a similar condition. Examination revealed a distinct cyst forming around the crown of the unerupted left mandibular first premolar (Fig 13). So far, no other cysts

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of this nature are evident, but careful check-up examinations will be made, from time to time, as other permanent teeth develop. No operation has as yet been performed on this patient.

In this family there are three other living children: two older brothers in the army and a sister still in school, who have been examined and show no evidence of dentigerous cysts. Two brothers died in infancy, one having been born with a cleft palate.

For the family histories and follow-up examinations in these four members of the same family, I am indebted to the Harrisburg Hospital and to the family dentist, Dr. J. Reese Beyrart, of Steelton, Pa.

TABLE II  
TABULATION OF AUTHOR'S CASES OF MULTIPLE DENTIGEROUS CYSTS

Case Nos	Sex	Age	Location of Cysts	
1	F	14	3 in maxilla 2 in mandible	
2	F	18	1 in maxilla 3 in mandible	
3	F	12	4 in mandible	Children of same family
4	M	11	2 in maxilla 1 in mandible	
5	F	10	2 in mandible	
6	F	8	At least 1 in mandible More may develop	

I have seen several other cases of multiple dentigerous cysts, and have lantern slides made from roentgenograms, but no names were attached and I have been unable to find the records, therefore, they are not included in this communication.

One rather unusual case of a combination of a dentigerous cyst with an adjacent dental root cyst is of interest.

**Case Report**—A female, colored, age 26, applied for treatment in October, 1934. For about two years she had complained of periodic swellings in the region of the left angle of the mandible, with slight pain and a discharge of pus from the gum. Examination showed the gum to be slightly congested behind the left mandibular second molar, and pus came out through an opening where the third molar should have been. Roentgenologic examination revealed the third molar unerupted, inverted, and its crown surrounded with a cystic cavity. In front of this, beneath and involving the roots of the first and second molars was a second large cystic cavity, extending almost to the lower border of the mandible (Fig. 14).



FIG. 14.—Radiograph showing dentigerous cyst connected with inverted left mandibular third molar and also a root cyst beneath the second and third molars.

This evidently was a root cyst connected, primarily, with the first molar, which had a large filling over a dead pulp

*Operation*—Through an incision in the mucous membrane, two separate cystic cavities were found, one surrounding the crown of the unerupted third molar and extending high up in the ascending ramus almost to the condyloid process, the other beneath and involving the roots of the first and second molars. The lining of the cysts was shelled out, the three molar teeth were extracted, and the bone cavities treated first by packing and later by irrigation

## SUMMARY

(1) Dentigerous cysts usually occur singly in individuals and are not uncommon

(2) Multiple dentigerous cysts have been occasionally reported

(3) Multiple dentigerous cysts in members of the same family are apparently extremely rare. The writer could find only one instance of this occurrence recorded in the literature

(4) Three children of the same family, with probability of a fourth, are herewith recorded as having multiple dentigerous cysts

(5) The treatment of these cysts is enucleation of the epithelial lining, with or without removal of the unerupted teeth involved. The prognosis is good, provided the lining is removed

(6) No explanation for the development of multiple dentigerous cysts is offered

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# PULSATING, BENIGN GIANT CELL TUMORS OF BONE

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NILATON,<sup>1</sup> in 1860, included a group of extremely vascular tumors of bone in his classical description of the giant cell tumors. One case occurring in the upper end of the tibia pulsed. The leg was amputated and the patient was reported to be alive and well more than eight years later.<sup>2</sup> During the next 50 years a number of papers on aneurysm of bone appeared. Examination of some of these tumors showed large blood spaces without evidence of neoplastic tissue, while others were frank tumors. Pulsation was noted in both types. Gross,<sup>3</sup> Gaylord,<sup>4</sup> and Le Dentu<sup>5</sup> concluded that the majority, if not all, of the benign bone aneurysms were the end-result of neoplasia. It is difficult to evaluate the cases reported by these investigators. No uniform basis for classification of bone tumors had been adopted. The surgery of the era frequently led to postoperative death. The survivors sometimes showed subsequent evidence of malignancy by recurrence and metastases. It is not surprising that confusion existed when the current difficulties encountered in the diagnosis of bone tumors are considered.

The modern literature contains very few references to the more vascular giant cell tumors. Ewing<sup>6</sup> discusses the aneurysmal type stating that expansile pulsation may be observed. He also points out that "these lesions do not do particularly well with irradiation and generally terminate in amputation."<sup>7</sup> Nové-Josserand and Taveirne<sup>8</sup> express surprise that so few cases of pulsating giant cell tumor have been reported in the American literature. This lesion appears to be more common in France though the four cases to which they refer could not be found (Roughton, Borst, Luecke, Schleich). Geschickter and Copeland<sup>10</sup> fail to consider the group. The standard textbooks and more extensive surgical reference works rarely more than mention the possibility of pulsation in the benign giant cell tumor of bone.

The condition is extremely rare. Only four cases of pulsating giant cell tumor that can be definitely identified as benign have been found in the American literature since 1900. None of the available foreign literature contains any reported cases that we have been able to find. More than 300 benign giant cell tumors have been studied from the bone sarcoma registry of the American College of Surgeons. Pulsation is not recorded in any of them though its absence is noted frequently. It is probable that many cases have not been reported. The lesion is important to the study of bone oncology.

since it may well represent a transitional phase between the benign and malignant tumors. A recently observed case is added to those collected from the literature.

### CASE REPORTS

**Case 1**—(Bloodgood<sup>11, 13</sup>) Three months after an injury, a white man, age 26, complained of pain and swelling in the lower radius. The tumor pulsated. The arm was amputated. The bony shell of the tumor was completely destroyed. Tumor tissue had broken through the capsule into the region of the carpal bones. The tissue was soft, friable, very vascular and was disintegrated by hemorrhage. Microscopically the lesion was a giant cell tumor with hemorrhage. The patient was living and well 20 years later.

**Case 2**—(Bloodgood<sup>11, 12</sup>) A colored female, age 45, had noted a tumor of the forearm for one year. It had been painful for nine months. It pulsated. Resection of both bones of the forearm was performed by Doctor Halsted. The tumor mass was subperiosteal, surrounding the shaft of the lower third of the ulna and infiltrating the muscle slightly. The bone was eroded. Microscopically the tumor was a "pure giant cell sarcoma." The stroma between the giant cells was very vascular. More than 15 years later the patient was living and well.

**Case 3**—(Cushing, reported by Lewis<sup>14</sup>) A boy, age 16, complained of pain in the lower dorsal and lumbar regions following a scuffle with a playmate. One year later a mass appeared in the back which gradually grew larger and became very tender. Weakness of the legs developed. At operation the tissues were more vascular than usual. In the lumbar spine a vascular, pulsating, soft, reddish tumor was found. It was covered by a thin shell of bone. The neoplasm was partially removed and roentgenotherapy instituted. Histologic examination of the tissue revealed cartilage and bone with spaces in between containing a coarse fibrous tissue in which were numerous multinucleated giant cells. The tissue between the bone spicules did not appear very vascular. The patient was alive and well seven years later.

**Case 4**—(Morton and Duffy<sup>15</sup>) A white male, age 30, fractured his femur two months before admission to the New Haven Hospital. He had refractured the bone at the same site. Roentgenograms showed marked callus formation. The leg was immobilized in a plaster encasement. During this time he complained of pain. Two months later bony union had occurred, but a soft elastic mass 5 cm. in diameter was found just below and internal to the patella. This corresponded to an area of bone destruction in the internal part of the head of the tibia extending into the shaft as seen on roentgenologic examination. A distinct pulsation\* was demonstrated in the tumor which was stopped by compression of the femoral artery. Repeated aspirations withdrew blood which clotted readily. A mid thigh amputation was performed. The mass was about the size of a baseball. It was well encapsulated, yellowish-brown, mottled with hemorrhagic areas. Histologically it proved to be a xanthomatous variant of a benign giant cell tumor. The patient was alive and well 14 years after operation.

**Case 5**—(R. M. H., No. 120513) B. R., white, female, age 52, Jewish, was admitted to the Rochester Municipal Hospital October 22, 1936, complaining of a painful mass in the back which had been present about six months. No family history of neoplastic disease could be obtained.

When a child, the patient had had smallpox which had resulted in a corneal scar. She had had pneumonia in 1921, and had been in ill health for 13 years. In 1924, she was hospitalized elsewhere because of inability to walk. A clinical impression of spinal cord tumor led to a laminectomy, at which swelling of the cord in the upper dorsal

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\* In the original report the pulsation was considered to be transmitted from the popliteal vessels.



region was found. This was interpreted as indicating an intramedullary neoplasm. The operation was followed by complete spastic paraplegia with a sensory level at the sixth dorsal segment. At this time she became addicted to narcotics. A prolonged course of roentgenotherapy was instituted and in two years the patient was able to walk. Sphincter control returned. Sensation became normal. An ulcer of the skin which never healed completely developed at the site of irradiation in the dorsal region. Menopause occurred at 51.

In April, 1935, 18 months before admission, the patient first noted tenderness in the left sacro-iliac region. Pain appeared, became constant, was aggravated by walking, and occasionally radiated to the lower abdomen and to the anterior aspect of the left thigh. In April, 1936, one year after the onset of pain, she accidentally discovered a swelling in the painful area. This grew slowly until she was able to feel the mass when fully clothed. Two months before admission she noted numbness and tingling in the feet. More recently she had difficulty in walking. The patient had experienced a "crackling" sensation at the tumor site.

*Physical Examination*—The patient appeared obese and moderately pale. Of chief surgical interest was a smooth, rounded, soft, fixed, nontender mass in the left sacro-iliac region measuring 8 cm in diameter. Pulsation in the mass was marked and was synchronous with the heart beat. A bruit was detected. Eggshell crackling was easily appreciated. The skin overlying the tumor was freely movable and slightly reddened. An elliptical ulcer (3.5 cm) was found along the upper dorsal spine. The edges were smooth and not indurated. The base was yellowish-red. Its maximum depth was 1.5 cm. The area was neither tender nor painful. A corneal scar was seen on the left eye, overlying a defect in the iris. Pyramidal tract signs were present bilaterally. No other neurologic signs could be made out.

The temperature, pulse and respirations were normal. Urinalysis showed nothing of pathologic import. The blood Wassermann was negative. A moderate secondary anemia was present.

*Roentgenologic Examination* of the pelvis revealed an irregular shadow of increased density extending medially and superiorly from the crest of the ilium to its posterior end. It was interpreted as indicating a large tumor (9x12 cm) overlying the left ilium and sacro-iliac joint and extending posteriorly some 3 or 4 cm (Fig. 1).

*Biopsy*—October 28, 1936. The tumor was biopsied and found to be an histologically typical benign giant cell tumor of bone containing numerous capillaries and blood sinuses (Fig. 2). Because of the relative inaccessibility of the mass a course of roentgenotherapy was instituted, 3,300 roentgen units being given through four portals over a period of 18 days. This produced no noticeable effect on either the size or the pulsation of the tumor.

*First Operation*—November 25, 1936. The tumor was partially excised. Everywhere vessels were found leading to the mass which lay beneath the fascia of the gluteus maximus. It bled profusely, appeared gray, and had the consistency of liver. It was completely encapsulated except where the biopsy had been performed. Electrosurgical methods were less efficient than usual, owing to the extreme difficulty in obtaining a dry field. Considerable quantities of tissue were removed by curettage but bleeding was so extensive that packing was necessary. Shock supervened and transfusion was given.

*Second Operation*—December 8, 1936. Further tumor tissue was removed. Saline solution, as near the boiling point as could be obtained, was injected into the mass without any effect on its pulsation or vascularity.

*Third Operation*—Ten days later (December 18, 1936) the third attempt at excision was made. Carbon dioxide snow and alcohol were used as hemostatic agents. The tissue froze very well but it was so hard that it had to be chipped out with a chisel which resulted in tearing of the contiguous tissue and fresh hemorrhage. Coagulation and looping proved to be the most efficacious means for removing the tumor. The patient was considerably shocked by this procedure, which necessitated transfusion. The



FIG 1—Lateral roentgenogram of left humerus. The thin rim of calcification indicates the extent of the tumor.

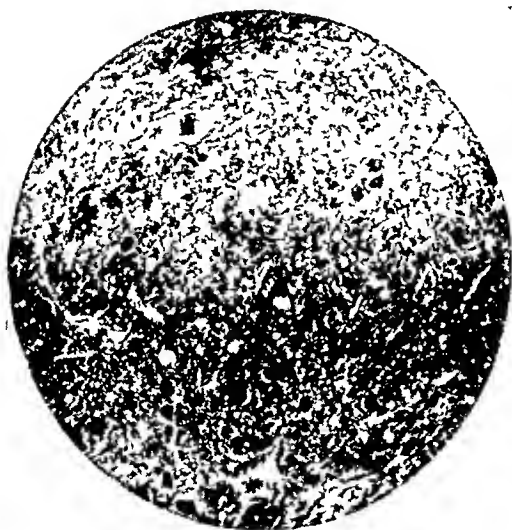


FIG 2—Photomicrograph of pulsating benign giant cell tumor of humerus. (Original biopsy specimen. (Original photo  $\times 100$ .)

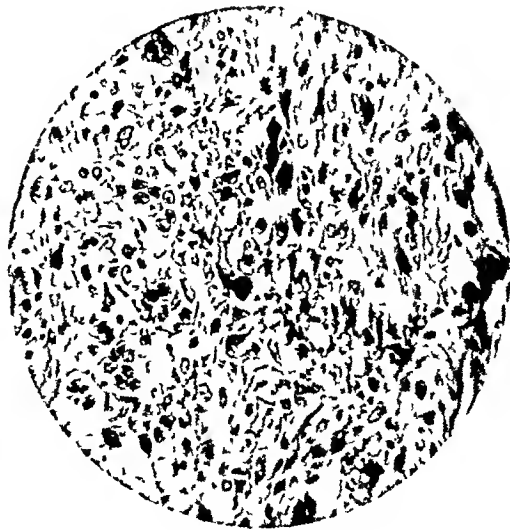


FIG 3—Photomicrograph of a so-called malignant variant of benign giant cell tumor. (From material removed March 22, 1937. (Original photo  $\times 650$ .)

operative incision was left open to permit the application of radium. On two occasions platinum needles were inserted. By this means a total of 960 mg hr was given to each of four sites. The tumor continued to pulsate.

*Fourth Operation*—March 22, 1937. The left internal iliac artery was ligated, which resulted in the immediate cessation of the pulsation. A considerable quantity of tissue was removed before the patient's condition became precarious. Pathologic examination of the tissue removed at this time showed the stroma to be less compact. The spindle cells were more irregular in size and shape and more hyperchromatic than formerly. This probably indicated a healing process or altered growth-rate rather than a malignant change. No mitotic figures were seen at any time (Fig 3).

*Fifth and Sixth Operations*—On April 17 and May 10, 1937, excision of the remainder of the tumor was accomplished. Many pockets were encountered extending into the soft tissues from which they were demarcated by a thin bony shell. The defect in the



FIG 4—Drawing to show the location of the tumor in the left ilium and the appearance of the bone defect after curettage.

ilium also showed the formation of pockets (Fig 4). Three Mikulicz pads could be placed in the cavity. It was filled with calcium salts and vitamin D. The total weight of the tumor excised was 400 Gm.

*Postoperative Course*—The patient made an uneventful convalescence and walked without difficulty. Granulations appeared slowly. When she left the hospital June 16, 1937, 237 days after admission, the cavity measured 8x8x6 cm. The wound continued to fill in during the summer. In September, 1937, difficulty in walking was noted, though physical signs in the lower extremities remained essentially unchanged. At this time the patient became depressed and expressed suicidal ideas.

She was hospitalized elsewhere during October but returned to Rochester Municipal Hospital November 6, 1937, unable to walk and with urinary incontinence. The operative site and the ulcer of the back appeared practically the same as when last seen. Bilateral spasticity of the lower extremities was present. Sensation was intact. The legs were weak but could be moved. She appeared mentally deranged.

Roentgenograms showed considerable new bone formation in the defect of the ilium without evidence of recurrence of the tumor. A biopsy taken from the granulating tissue showed no histologic evidence of neoplasia. One week after admission, the temperature rose and an area of inflammatory reaction appeared on the left buttock. Her condition thereafter grew progressively worse. Both upper extremities became spastic. Left lower facial palsy developed. The lungs showed no changes of pathologic significance on physical examination. The temperature rose to 41° C and the patient expired on her fourteenth hospital day. Permission for postmortem examination was refused.

The survival periods and the benign histologic pictures are ample evidence of the nonmalignant character of the cases collected from the literature. Case 5 lacks the confirmatory evidence of postmortem examination, yet no clinical signs of metastases or of recurrence could be demonstrated. The patient apparently died of a rapidly progressing intracranial lesion associated with signs of infection. The histologic examination of a large number of pieces of tissue revealed typically benign giant cell tumor. Two biopsy specimens from the healing wound showed no evidence of neoplasia. It is evident, then, that benign giant cell tumor of bone may pulsate.

The differential diagnosis of this tumor is difficult. Of the cases recorded, only two occurred in the epiphyseal regions. To these may be added Nelaton's case. Four of the patients were more than 25 years of age and two were more than 40. The available roentgenograms (Cases 4 and 5) do not show the characteristic cortical expansion and trabeculated area of decreased density commonly associated with benign giant cell tumor. That this neoplasm may produce an osteolytic picture has been demonstrated by Kirklin and Moore<sup>16</sup>. Two cases (Cases 1 and 4) developed rapidly in a few months. The histories of the others occupied more than a year.

Pulsating, benign giant cell tumor resembles a form of malignant bone tumor with which it is frequently confused. Ewing<sup>6</sup> includes this neoplasm among the telangiectatic osteogenic sarcomata. Geschlucker and Copeland<sup>10</sup> discuss it as osteolytic sarcoma. It is a central lesion eroding the bone at or near the epiphysis. Periosteal reaction may be seen. The history extends over several years. Histologic examination shows characteristic multinucleated giant cells of the foreign body type. The fibrous elements are anaplastic. Whether or not a lesion of this type may be justifiably included among the telangiectatic osteogenic sarcomata seems questionable. It has much in common with the giant cell tumor and may very well represent a truly malignant form of this neoplasm. The more common variety of osteolytic or telangiectatic sarcoma occurs most frequently in younger persons, destroys the shaft rapidly, extends into the soft tissues, and metastasizes early. The course of the disease is measured in months rather than years.

Bucy and Capp<sup>21</sup> reported eight cases of hemangioma of bone. None of these pulsated but pulsation was noted in three cases that they collected from the literature. Two of these occurred in the skull, the other, in the clavicle. In these the periphery of the tumor presented an area of bony hardness raised above the level of the surrounding bone, while the center was soft and pulsated. In long bones primary hemangioma appears roentgenologically

as "a loculated tumor with an interspersed fine fibrillary framework. The cortex is usually destroyed but may extend into the center of the expansive tumor. The periosteum, though expanded, remains intact." Hemangioma of the vertebrae rarely gives symptoms.

Carcinomatous metastases to bone may produce pulsating lesions. This is particularly true of clear cell carcinoma (hypernephroma) of the kidney<sup>17, 18, 24</sup>. Though generally multiple, metastatic renal carcinoma may be solitary. The lesions are found most frequently in the axial skeleton. They are of the osteolytic type and rarely involve an epiphysis. Pulsation has been recorded also in metastatic carcinoma of the thyroid,<sup>19, 24</sup> and in so-called malignant angio-endothelioma of bone.<sup>20</sup>

A clinical diagnosis of pulsating, benign giant cell tumor of bone would be extremely difficult and fraught with considerable danger if we recognize that all gradations of malignancy occur in giant cell tumors.<sup>8</sup> Though the nature of the lesion may be suspected, final classification must depend upon a thorough study of all the available data—clinical, roentgenologic, and pathologic.

The treatment of pulsating giant cell tumor involves special problems. When pulsation is detected on clinical examination, it indicates a dissolution of the bony capsule unless the tumor is originally subperiosteal. Ewing<sup>6</sup> has stated that these very vascular tumors are frequently refractory to irradiation. Surgery must first be aimed at hemostasis. The most effective means is by ligation of the blood supply. In the lower extremity this may be tantamount to amputation. The results of conservative treatment of giant cell tumors about the knee have been sufficiently discouraging to warrant primary amputation of these aggressive pulsating lesions. This is particularly true when it is recalled that metastasizing tumors, frank osteogenic sarcomata, have arisen at the site of benign giant cell tumors which, presumably, were inadequately treated. When suitably located, resection would appear to be the operation of choice. Curettage should be reserved for those cases that are radioresistant and are not amenable to other procedures.

It is difficult to draw far reaching conclusions from so small a series of cases. In 1919, Bloodgood<sup>13</sup> wrote "The color of the giant cell tumor must be due to its vascularity, yet pulsation has been noted in only two cases." Nevertheless, Codman<sup>22</sup> advanced the theory that pulsation was responsible for the centrifugal growth of central giant cell tumors. We believe that this position is untenable. Operators have written of the hemorrhage encountered from these tumors, of their excessive vascularity, but not of their pulsation. Numerous cases are found in the bone sarcoma registry in which the tumor has eroded through the bone and even fungated, yet the absence of pulsation is specifically recorded. In other cases very vascular giant cell tumors did not pulsate even though they were diagnosed aneurysmal. Case No. 1553 of the registry series showed no clinical evidence of pulsation even though the tumor mass was well filled by injection through the afferent artery.

The mere fact that a giant cell tumor may be visualized roentgenographically

after injection of its afferent vessels is not evidence of pulsation. Dos Santos<sup>21</sup> has studied the vascular pattern of some bone tumors by arteriography. He believes that the time elapsing before the veins are visualized is significant. In general, the more rapidly the opaque substance (thorotrast) appears in the efferent vessels, the more malignant is the tumor. In the benign giant cell tumors that he studied the time interval approximated that found in inflammatory lesions. In one case, clinically diagnosed benign giant cell tumor, an extremely short period elapsed leading to a diagnosis of malignancy which was subsequently confirmed. He describes large blood lakes in the giant cell tumor and notes that the thorotrast is retained by the lining cells for more than a month. He interprets this observation as lending support to the theory of the endothelial nature of the multinucleated giant cell.

The reason for the pulsation in benign giant cell tumors is obscure. It may be due to an arteriovenous communication or to an excessive arterial supply. No differences between the vascular pulsatile and nonpulsatile giant cell tumors can be demonstrated histologically. The diagnosis of pulsation must rest purely on clinical observation.

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# THE TREATMENT OF DELAYED UNION AND NONUNION OF FRACTURES BY SUBCUTANEOUS DRILLING

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RECENT improvements in the treatment of fractures have been largely confined to methods of reduction and fixation. Great strides have been made in the prevention of malunion, deformity and impaired function, but delay or absence of bony union still presents difficult problems. The increasing severity of injuries produced by modern machinery has more than kept pace with improvements in treatment. No attempt will be made in this paper to review the theories of repair of bone. It is generally agreed that the blood clot between and around the fracture-ends is organized by granulation tissue. Calcification of this fibrovascular framework is normally followed by restoration of the integrity and contour of the bone.

Failure of firm union within the accepted normal time for any particular bone may be considered as delayed union. This term implies that the physiologic processes of repair are still going on, and will eventually result in restoration of continuity of the bone. However, more than an arbitrary time limit is necessary for the diagnosis of nonunion. This term is applicable only when the process of repair has run its cycle back to the resting stage without the occurrence of bony connection between the fragments. That is, the raw bone-ends have healed over and the gap between the bones is filled with inactive soft tissue. Differentiation between delayed union and nonunion is of considerable importance since prolonged immobilization is justified in the former and will usually result in union if the bones are in approximation. Lack of immobilization at this stage may convert delayed union into nonunion. Clinical differentiation between delayed union and nonunion is often difficult. It is best made by careful roentgenologic study of bone detail at the fracture site. If the ends have healed over and smoothed off, with obliteration of the medullary canals, nonunion may be said to exist, without regard to the time involved.

Constitutional factors, such as diseases associated with malnutrition, may contribute somewhat to slow healing. From a practical standpoint, however, the causes of nonunion are local, that is, at the site of fracture. Except in rare instances, there are no constitutional or general causes and likewise no constitutional or general therapy effective for deficiency of union of bone. An important local cause of defective union is lack of approximation of the fragments, often due to interposed soft tissue. Separation of fragments by overly powerful traction especially skeletal traction-countertraction, is seen with increasing frequency. The prevention and correction of improper approximation is obvious. Impaired local blood supply plays an important part



in delayed union, and may be due to vascular disease, extensive soft tissue injury or the location of the fracture. Poor immobilization may allow shearing or angular stresses at the fracture site. The granulation tissue and vessels bridging the fracture are torn and calcification is prevented. Compression stress at right angles to the fracture line, however, aids union and is one of the advantages of ambulatory treatment. Open fractures, whether compound or operative, allow escape of the clot, which is the scaffolding for the building of callus. Undrained infection destroys growing tissue and is often an important factor. Well drained infection does not materially delay healing.

Aside from prolonged fixation, the treatment of delayed union lies in the reestablishment of a mild aseptic inflammation which will speed up repair. In true nonunion, conditions comparable to a fresh fracture must be restored. This implies revascularizing the sclerotic, healed-over bone-ends and replacing the intervening scar with granulation tissue. In addition the medullary cavities should be opened. Most methods of treatment which satisfy these requirements are major operative procedures which are only justifiable when a definite diagnosis of nonunion can be made. Subcutaneous drilling of fragments satisfies these requirements and is effective in promoting union. It is a minor procedure which is simple, safe, and does not interfere with ambulatory treatment.

Subcutaneous drilling was recommended over 40 years ago<sup>1</sup>. It was revived by Beck,<sup>2</sup> in 1929, and popularized by Bohler.<sup>3</sup> Carter,<sup>4</sup> and Easton and Prewitt<sup>5</sup> have reported favorable results, and Bozsán<sup>6</sup> has stressed its value. By this method numerous narrow channels are made across the fracture site, perforating the sclerotic bone-ends and scar and opening the medullary canals. These channels connect endosteum and periosteum and are filled with a mixture of blood clot, bone dust and bone marrow, which is excellent fertilizer for callus. Capillaries growing along the drill-holes can revascularize the sclerotic bone and scar tissue. The procedure may be carried out under general, regional or local anesthesia. I have preferred spinal anesthesia for the lower extremity. The drill which I use is a three or four inch length of large Stille-Kirschner wire. This drills a channel about 2 mm in diameter and is flexible enough to avoid the danger of breakage.

The technic is simple. After preparation of the skin, the fracture site is localized by palpation or measurement from roentgenograms. The drill-point is inserted directly through the skin on one side of the limb about one inch above the fracture. Ten or 12 drill-holes are made, radiating fan-wise across the fracture. A similar number are made from a point below the fracture and through two perforations on the opposite side of the limb (Fig. 1). About 40 channels should be made through four skin perforations in a bone the size of the tibia. In fractures of the leg, oblique osteotomy of the healed fibula may be necessary in order to approximate the tibia. After drilling, a sterile dressing and a nonpadded plaster encasement are applied. Ambulatory treatment is resumed in about 48 hours. Serial roentgenograms usually show early decalcification of the sclerotic bone, which indicates increased

vascularity. This is followed by the appearance of callus between and about the fragments, bridging the previous gap.

During the past two and one-half years I have carried out subcutaneous drilling in 12 cases of delayed union or nonunion of the tibia at intervals of from two months to two years after injury. The safety and simplicity of this method have justified its use at an earlier period than would have been advisable for an operation of greater magnitude. Drilling in early delayed union, such as obtained in Cases 8, 11 and 12, has quite likely prevented frank nonunion. Union has occurred in all instances and it has not been necessary to resort to any more radical procedure. The only complication has been the recrudescence of a mild infection in a compound fracture treated nine months after the accident. This infection was due to the fact that drilling was carried out only two months after healing of the last sinus. It did not interfere with union.

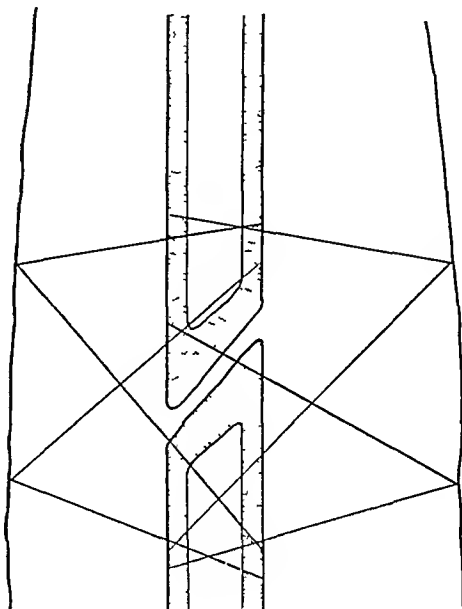


FIG 1—Diagram showing the cone shaped areas covered by drill holes through each of four skin punctures. About ten channels are distributed through each sector, making a total of 40 perforations through the region of the fracture.

### CASE REPORTS

Case 1—W. W., white, male, age 30, sustained a spiral fracture of the left tibia and fibula, January 26, 1935. There was no evidence of union on May 10, 1935, three and one-half months after injury. Subcutaneous drilling was carried out at this time. Two months later, July 17, 1935, there was firm union, and unaided weight bearing was resumed (Figs 2, 3, 4).

FIG 2

FIG 3

FIG 4



FIG 2—(Case 1) Wide separation of the tibia with no callus three and one-half months after injury.  
FIG 3—(Case 1) Immediately after drilling and osteotomy of fibula showing multiple perforations.  
FIG 4—(Case 1) Abundant callus between and around the fragments two months after drilling.

Case 2—E. B., white, male, age 34, had a crushing fracture of the right tibia and fibula, November 29, 1934. There was no evidence of union on May 25, 1935, six months

after injury, when drilling was carried out. On October 30, 1935, union was firm enough for unaided weight bearing.

**Case 3**—G H, white, male, age 61, sustained a compound comminuted bumper fracture of the right tibia and fibula, December 29, 1933. He was treated by debridement, primary closure and ambulatory plaster encasement. There was nonunion of the tibia on January 7, 1935. At this time resection of the fibula was carried out and ambulatory treatment continued. Nonunion persisted and, on June 26, 1935, drilling was performed, 18 months after injury. All external support was removed on January 22, 1936, at which time there was firm union.

**Case 4**—C R, white, male, age 56, sustained a compound comminuted fracture of the right tibia and fibula, October 15, 1933. Marked arteriosclerosis was present. Debridement and primary closure resulted in sloughing of the skin flaps but no bone infection. On June 20, 1934, the fibula was resected on account of nonunion. This resulted in weak, partial union with spontaneous refracture on September 25, 1935. Drilling was carried out on October 4, 1935, two years after the accident. On June 10, 1936, union was firm enough for unsupported weight bearing.

Fig. 5

Fig. 6

Fig. 7

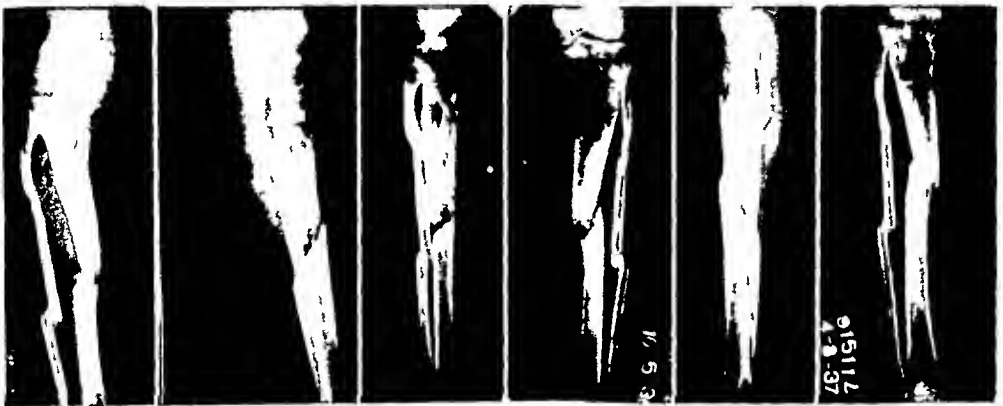


FIG. 5—(Case 6) Nonunion of compound fracture of tibia 15½ months after injury.  
FIG. 6—(Case 6) Immediately after drilling showing perforations through fracture site.  
FIG. 7—(Case 6) The fracture line has bridged over and is almost obliterated.

**Case 5**—O B, white, male, age 55, sustained a fracture of the left tibia and fibula, November 15, 1935. There was no evidence of union on February 27, 1936, when drilling was carried out, three and one-half months after injury. There was good union on October 2, 1936, and the patient was bearing full weight on the leg.

**Case 6**—S K, colored, male, age 36, received a compound comminuted fracture of the left tibia and fibula by crushing injury in a mine accident, June 22, 1935. There was a frank nonunion when he was seen on September 22, 1936. Drilling was carried out October 5, 1936, 15½ months after injury. There was solid bony union on June 22, 1937 (Figs. 5, 6, 7).

**Case 7**—J G, white, male, age 20, was seen July 8, 1936, with a compound fracture of the right tibia and fibula of seven weeks' duration. Ambulatory treatment was carried out. There was no evidence of union on October 23, 1936, when drilling was performed, five months after injury. On September 30, 1937, union was firm and the patient was bearing full weight without support.

**Case 8**—E F, white, male, age 52, received a compound fracture of the left tibia and fibula on September 5, 1936. Debridement and closure were followed by ambulatory treatment. There was no evidence of union on December 11, 1936, three months after the accident. Subcutaneous drilling at this time resulted in firm union and unaided weight bearing by March 17, 1937.

**Case 9**—E P, white, male, age 41, received a compound bumper fracture of the

## DRILLING OF FRACTURES

left tibia and fibula on February 25, 1936. Debridement and closure were followed by ambulatory treatment. There was no evidence of union on December 11, 1936, nine and one-half months after the injury. Drilling was carried out at this time and resulted in firm union by March 16, 1937 (Figs 8 and 9).

**Case 10**—J. T. F., white, male, age 59, received a compound crushing fracture of the right tibia and fibula in a mine accident in September, 1936. When seen on June 11, 1937, nine months after the accident, frank nonunion was present. Drilling was carried out at this time. There was marked arteriosclerosis. By October 6, 1937, fair union was present and the patient was walking with a brace.

**Case 11**—J. H., white, male, age 45, with marked arteriosclerosis, received a crushing fracture of the left tibia and fibula, June 3, 1937. There was no evidence of union two months after the accident. Drilling was carried out August 13, 1937. On October 4, 1937, union was firm enough for weight bearing with a brace. The patient was walking without external support, November 30, 1937.

FIG 8

FIG 9

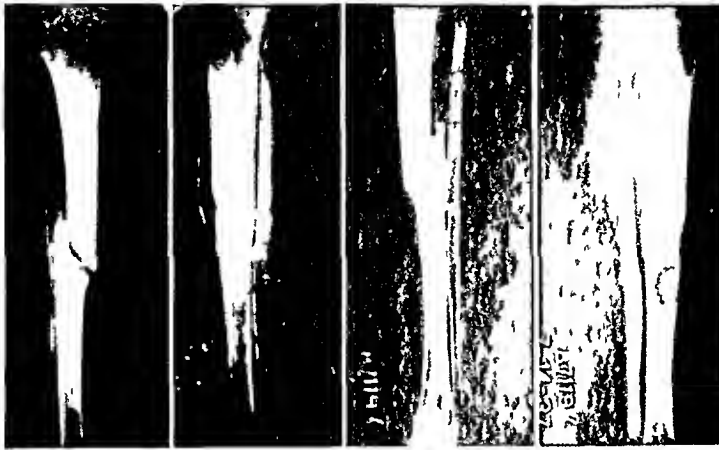


FIG 8—(Case 9) Nonunion of tibia at time of drilling, nine and one-half months after injury.

FIG 9—(Case 9) Seven months after drilling. Good clinical union was present and all external support was removed three months after drilling.

**Case 12**—J. L. S., white, female, age 61, sustained a bumper fracture of the right tibia and fibula with extensive soft tissue damage and a compound fracture of the right radius and ulna, July 25, 1937. Two months after the accident there was good union of the forearm but the fracture of the leg showed no evidence of union. Drilling was carried out September 23, 1937. On November 18, 1937, fair union was present and the patient was fitted with a brace.

### CONCLUSIONS

- (1) Subcutaneous drilling of fragments is a safe, simple and effective treatment for delayed union and nonunion.
- (2) It does not interfere with ambulatory treatment.
- (3) These qualities justify its use in early cases before more radical methods would be considered.

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#### DISCUSSION OF THE PAPERS OF DOCTORS GILCREST, CARROLLS AND GRISWOLD

DR ERNEST SACHS (St Louis, Mo) —There is no question that there are a large number of causes for lumbosacral and sacro-iliac pain. There is one condition to which attention has been drawn which I think should be emphasized, because I believe it is much more common than is generally recognized, namely, dislocation of the nucleus pulposus. There is no question that a great many of these cases of obscure pain, sciatica or pain on both sides, sometimes associated with bladder disturbance, have as their cause dislocation of the nucleus pulposus, and the only way to cure it is to make the diagnosis and then remove the cause. The diagnosis is very difficult, in fact, I do not know of any group of symptoms which are absolutely characteristic of dislocation of the nucleus pulposus. The only way to be certain is to obtain a roentgenogram, employing lipiodol, with the patient lying on the abdomen. I do not mean that in a case of sacro-iliac or lumbosacral pain this is the first thing to look for. Certainly the simpler methods of fixation are very desirable and should be used, but if they do not give relief this other condition should be looked for.

A case in point was that of a farm hand who had had pain for seven or eight years. Prior to that time he had had bladder disturbance for 14 years. He presented the typical picture of lumbosacral disturbance and was referred to an orthopedist who employed the usual methods of fixation. These were tried for a month or six weeks with no relief, and when he came back we made a systematic study of the bladder, and the urologist reported a neurogenic bladder. A roentgenogram following the injection of lipiodol revealed a marked dislocation of the nucleus pulposus at the junction of the fourth and fifth lumbar articulation, which was removed. The symptoms promptly cleared up. If the orthopedic surgeon will become more nucleus pulposus minded, we will find many more such cases.

DR WILLIAM A BOYD (Columbia, S C) —With reference to fixation of fractures of the femoral neck, the pendulum has swung decidedly toward internal fixation, and many methods of procedure have been advanced. While we believe that we are assured of better final results as regards bony union by internal fixation, through the elimination of the long period in bed, the plaster encasement, the dressings, and the ability to give early motion to the limb and early physical therapy, still we may not, as yet, make that an unequivocal statement. We cannot expect to obtain perfect results in all cases, there will always be some deaths, some nonunions, and a certain percentage in which there is an aseptic necrosis of the femoral head. We do hope by this means of internal fixation to obtain more perfect bony union and in a much greater proportion of cases. Complete immobilization and anatomic apposition of the fragments are absolutely essential for bony union. The latter is best obtained by Leadbetter's method of reduction, the former can be obtained by screws, nails, pins or whatever the surgeon deems advisable and is most familiar with.

We must remember that fractures of the femoral neck are serious surgical injuries, and the repair of the fracture is a major surgical procedure and the patient should receive appropriate postoperative treatment. Weight bearing should not be permitted until we are sure of bony union, the photograph

of the patient walking with crutches within 24 or 48 hours after operation is an excellent advertisement, but indicates poor surgical judgment, and in the end the patient will pay the bill

DR JOSEPH E J KING (New York, N Y) —The conditions described by Doctor Gilcreest, are the causes of much concern to Dr Philip Wilson and his staff at the Hospital for the Ruptured and Crippled. I should like to mention one other condition in the sacro-iliac joint which produces symptoms similar to those described, namely, a suppurative lesion in the joint

An illustrative instance occurred in a boy, age 18, who presented himself, in 1922, with an abscess pointing in the left groin. This was drained by one of the local surgeons, but the sinus failed to heal. Roentgenograms failed to demonstrate a lesion in the sacro-iliac joint. After injecting the sinus with bismuth paste, the roentgenogram showed that the sinus extended to a point just in front of the sacro-iliac joint. The sinus was laid wide open and curetted, without entering the peritoneal cavity. After a prolonged convalescence it finally healed, but opened spontaneously nine months later. Roentgenograms still failed to show any lesion in the joint. After about two months the sinus again healed.

In January, 1924, a large, subgluteal abscess formed on the left side beneath the buttocks, and pointed in the gluteal fold. This abscess was widely opened and exploration revealed that the floor of the abscess was formed by the sacrum and the sacro-iliac joint, but no exposure of denuded bone could be determined. The remaining sinus did not heal.

In June, 1924, the anterior wound again opened spontaneously. The tract was injected with a radiopaque medium, and roentgenograms showed that the tract led backward and upward to a point just anterior to the left sacro-iliac joint. This sinus was opened and explored throughout its extent, and healed about a month and a half later. The posterior sinus did not heal.

In December, 1925 roentgenograms showed three foci in the left sacro-iliac joint about one inch apart, each about the size of a shirt button. These lesions were considered to be suppurative foci, and it was believed that they were the cause of the abscesses which formed, first anterior to the joint, and then posterior to it, breaking through first on one side and then on the other.

Dr William A Rogers, of Boston, then operated upon the case, making a curved incision along the crest of the ilium, exposed the posterior surface of the left sacro-iliac joint by stripping the musculature off, and opened the joint widely. The three suppurative foci, each about 1 cm in diameter, were found at the sites shown on the roentgenogram. Each small abscess cavity was filled with thick granulations and contained about five or six drops of pus. All of the bone was removed except a small bridge connecting the ilium to the sacrum.

The wound was dakinized, and later a plastic operation was performed. The cavity was filled with a muscle flap, and the skin incision was closed. It healed kindly without further infection, and both sinuses, the anterior and the posterior, healed.

In this instance, the sciatic pain and the pain in the region of the sacro-iliac joint was produced by the three small suppurative foci in the joint.

DR JAMES S SPEED (Memphis, Tenn) thought that Doctor Gilcreest's idea of very careful consideration of the history of these cases, combined with routine physical examinations was a helpful solution of many of these problems. In spite of all the methods we have for diagnosing them—history, physical examination, roentgenogram, *etc*—he thought we were still at a loss many times to differentiate between lesions of the lumbar spine,

the lumbosacral joint and the sacro-iliac joint. Especially in medicolegal and compensation cases, was it desirable to form a definite opinion in regard to the injury and give a positive report on it. Unfortunately, in many cases this is impossible, for even with all the data assembled one cannot state definitely whether the lesion is feigned or actual.

In regard to the question of moving or slipping in the sacro-iliac joint, there is a great difference of opinion. We all must admit there is no gross displacement except where it is actually demonstrated roentgenologically. We will have to admit, however, that, in certain cases, severe pain localized in the sacro-iliac joint is completely and immediately relieved by manipulation. This has been proved in many cases by manipulations performed by cultists of various types. There must be a slight movement in these joints which, when the surfaces are roughened, permits sufficient disturbance in the normal meshing of the surfaces to produce pain and by manipulation this slight change in position is corrected. As our methods of diagnosis become more accurate, we will be able to end uncertainty.

Various methods of internal fixation for central fractures of the neck of the femur have entirely changed the procedure for treatment of this severe injury. In previous methods of treatment, of which that by Whitman was the best, statistics of the majority of writers gave an average of 50 to 55 per cent solid bony union. The period of convalescence was extremely trying and often fatal in old, debilitated patients. The percentage of unions has increased to approximately 80 per cent with internal fixation and convalescence is relatively uneventful.

In regard to drilling of delay union and nonunion in fractures, there is considerable evidence to show that in delayed unions drilling unquestionably promotes callus production and hastens union, and probably will turn the table in many cases between a union and a nonunion. In typical nonunion, however, he did not think it was a reliable method. It may accomplish results sometimes but with the majority of typical nonunions a more definite method of bone grafting should be employed.

DR EDGAR L. GILCREEST (closing).—It is interesting that similar strains or slips occur in the facets of the vertebrae in the cervical region as in the lumbar region and can be relieved easily by manipulation. He had manipulated a number of patients for this condition with immediate relief of pain and relaxation of the unilateral spasm which had been producing a wry neck. During this manipulation some of these patients, as frequently happens in patients being manipulated for low back pain, often feel and hear a snap.

DR RALPH G. CAROTHERS (closing).—He wished particularly to emphasize the fact that in all cases in which the pins have been placed through two good bony surfaces, they have not loosened. When this was not done sometimes they have loosened.

Where tissue has been cut crossways, there is a little slough, and if one puts on a plate early in the case he is bound to have the fragments separate. That is the reason plates have been accused of being the cause of nonunion—because they prevented the small amount of collapse that Doctor Griswold spoke of.

In regard to Doctor Gilcreest's paper, he thought one can have a sacro-iliac pain without there being a Krocming sign. If the ilium is rotated forward on the sacrum it does not cause a Krocming sign. He had had some difficulty occasionally in removing the bolts, notwithstanding the fact that two kinds of metal had been used.

## BRIEF COMMUNICATIONS AND CASE REPORTS

### GIANT FACETED CALCULUS OF THE APPENDIX

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BEING without teeth, fowls swallow small stones into the tough gizzard which by rhythmic muscular contraction grinds them with the food, softening it for digestion. The grinding sounds may be heard when the ear is placed near the gizzard of a chicken after it has been fed and the movement of the stones may be seen in the fluoroscope. Although of extrinsic origin, the stones have physiologic function. Because it has stones in the stomach a fish in Ireland has been named the Gizzard Trout. Bland-Sutton<sup>1</sup> says stones are common in the stomachs of crocodiles and that pebbles in large quantities may be found in the stomachs of seals and sea lions.

Intrinsic stones sometimes form as calcareous concretions about nuclei of vegetable matter in the large intestines of cattle. In the middle ages such stones from the deer were considered henlooms and were preserved in gold cases as amulets because of miraculous healing power they were supposed to possess. Sir Walter Scott's book, *The Talisman*, is based on this myth. Prescribed even for leprosy and plague, the bezoar stone<sup>2</sup> as a prophylactic and therapeutic remedy may be found in the London pharmacopoeias until the mid-eighteenth century. Even in America in an earlier generation so-called "mad stones" from the intestines of animals were applied to wounds from the bites of rabid animals to withdraw the poison and thereby prevent hydrophobia. This hysteria lasted until the final acceptance of Pasteur's work.

In the human, stones that form in the alimentary tract are rare. In a young man who had died of acute perforation of a pyloric ulcer, we found a mass of kaolin in the stomach, molded by muscular contraction to conform to the pyloric outline. The ulcer had probably come from pressure, the kaolin having accumulated in the stomach after it had been eaten from time to time by the patient as his perverted taste demanded. Neither gallstones that have passed into the bowel nor hard masses of inspissated feces are true intestinal calculi. However, rarely small dark concretions of calcium phosphate or magnesium phosphate, discolored by fecal pigment, and called intestinal sand by Adam,<sup>3</sup> are found in the colon.

Since the original description of appendicitis by Reginald Fitz,<sup>4</sup> in 1886 observers have repeatedly confirmed his finding of the incidence, 59 per cent in the autopsies performed by him, of fecal concretions in the appendix, especially in the cases with gangrene and perforation. Wangensteen and



Bowers,<sup>5</sup> in a recent study of acute appendicitis, found appendoliths in 44 per cent of the suppurative cases, and in 80 per cent of the cases with gangrene. Being closed at the distal end, there is no fecal stream in the appendix as in the intestine. Material entering it can be expelled only by reverse peristalsis. When there is partial obstruction at the base, retained feces are often, by attempts at expulsion, molded into one or more rounded masses which, becoming dry and hard, block the lumen and shut off the blood supply of the



FIG. 1—Photograph of the unopened appendix.



FIG. 2—Roentgenogram of the unopened appendix showing stones.

appendix, which is terminal, thereby causing inflammation and gangrene. Royster<sup>6</sup> says, in appendicitis the fecalith plays the dual rôle of cause and effect.

In contradistinction to the ordinary fecalith, a true calculus of the appendix is rarely encountered, having been found by us only once in over 2,000 cases. Although some secretory matter may be included, it is composed mainly of mineral salts that have been deposited, usually about a nucleus of organic matter. Neither the kind of food nor the water taken by the patient is an active factor. Its formation is preceded by a catarrhal inflammation of the appendix with repeated outpourings of mucus into the lumen from which, because of chronic stasis, inorganic salts are deposited. As it enlarges, the

obstructing calculus causes additional inflammation with more active secretion of mucus, so that a vicious cycle is established. In the mucosa of the appendix, as of the colon, Lieberkuhn's glands or follicles are described as being so numerous that they form almost a continuous layer. The glands are composed of spherical secreting cells many of which undergo mucoid distention and become goblet cells.<sup>7</sup> When there is obstruction, the secretion of these cells may accumulate in the lumen, converting the appendix into a retention cyst



FIG 3—Photograph of the appendix opened, showing stones

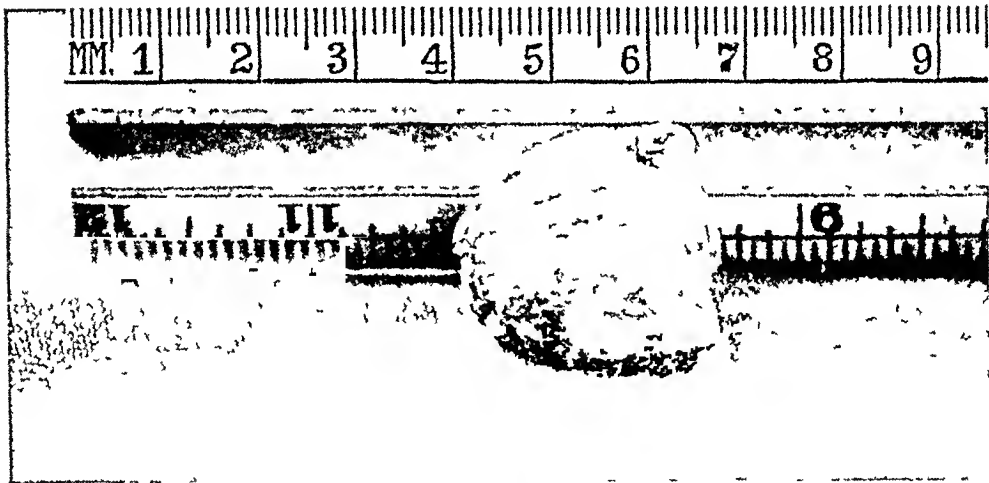


FIG 4—Photograph of the large faceted stone

or mucocele, the contents of which, if rupture occurs, escaping into the peritoneal cavity, may cause pseudomyxoma peritonei.

Most large calculi of the appendix when sectioned are found to be laminated. However, even when acute inflammation and perforation have not occurred, most stones cause symptoms which, under modern conditions, are sufficient to demand the removal of the appendix while the stone is yet too small for this effect. Royster gives Packard,<sup>8</sup> in 1921, credit for having had the largest appendix stone on record, measuring 12x4 cm and weighing 8

Gm It was found in a man, age 62, and protruded through a ragged hole in the appendix made by pressure necrosis, and had not caused suppuration. Since 1921 no case has been reported which has approached this in size.

**Case Report**—F L S, white, male, age 61, was admitted to the South Carolina Baptist Hospital May 4, 1936, complaining of pain and soreness in the right abdomen near the naval. The discomfort had begun two years before with attacks of indigestion and generalized pain over the abdomen. There had been nausea but never vomiting. From constipation and loss of appetite he had lost considerable weight.

*Physical Examination* showed him to be poorly nourished with negative findings except moderate tenderness over the right lower abdomen and a hard, slightly movable mass in this region. Temperature, normal. Leukoocytes, 11,000, 74 per cent polymorphonuclears. Hemoglobin, 79 per cent. Urine, normal.

*Operation*—May 5, 1936. The abdomen was opened through a McBurney incision. Instead of malignancy of the cecum which had been considered, the appendix was found without inflammation and without adhesions but with the distal end so large and so hard that it appeared to be a calcified mass the size of a lemon attached by a pedicle to the cecum which itself, however, was normal in every way. Appendectomy was performed, which was followed by an uneventful convalescence.

*Gross Pathology*—The appendix when opened was found to contain a giant calculus in the sacculated distal end with four smaller calculi nearer the base. All five were faceted and of shapes suggesting early segmentation with displacement of the smaller fragments of a parent stone that had originally extended most of the length of the appendix. The wall of the appendix about the large stone was very thin with the muscular layer absent. There was no ulceration of the mucosa or evidence of inflammation. Indeed, the mucosa, except about the large stone, was hypertrophied. The large stone weighed 13.5 Gm and consisted of calcium phosphate and magnesium phosphate with traces of organic matter.

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## PLASTIC REPAIR FOR POSTOPERATIVE ANAL INCONTINENCE

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ANAL incontinence is a most distressing and incapacitating condition. Hirschman said "The anal sphincter is one of the most important muscles

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in the body, and probably the most important sphincter muscle guarding as it does the outlet of the gastro-intestinal canal. Anything which interferes with its integrity interferes with the very enjoyment of life and happiness.

There are many causes that may interfere with its action and cause partial or total incontinence. They are usually grouped as (1) Central nervous disease and nerve injury (2) Anorectal disease (3) Injuries (4) Operative results

In the present communication we are concerned with postoperative incontinence. The most usual operation causing incontinence is fistulectomy. Fistulectomy seldom causes incontinence posteriorly but is frequently found in the lateral segments, especially following operation where the muscle has been undermined and without the proper support, and commonly by the use of prolonged packing. Such a type of incontinence is ideal for the employment of the procedure herewith detailed.

Attempts at plastic repair were undertaken many years ago, including operations for various forms of lack of sphincteric function, such as those reported by Ranschoff,<sup>1</sup> Steindl,<sup>2</sup> Clittenden,<sup>3</sup> Gobells,<sup>4</sup> Sistiunk,<sup>5</sup> Hirschman,<sup>6</sup> and Izquierdo.<sup>7</sup> In the more recent literature there have been several outstanding contributions. Previously the mode of attack was plastic repair of the muscle. There have been many successful operations of this type suggested which have had as their aim the approximation by suture of the ends of the severed muscle. In recent instances it can be accomplished, but the majority of cases are seen late, and in the meantime the muscle has retracted, atrophied, and degenerated into fibrous tissue. As a whole, these procedures have not been too successful.

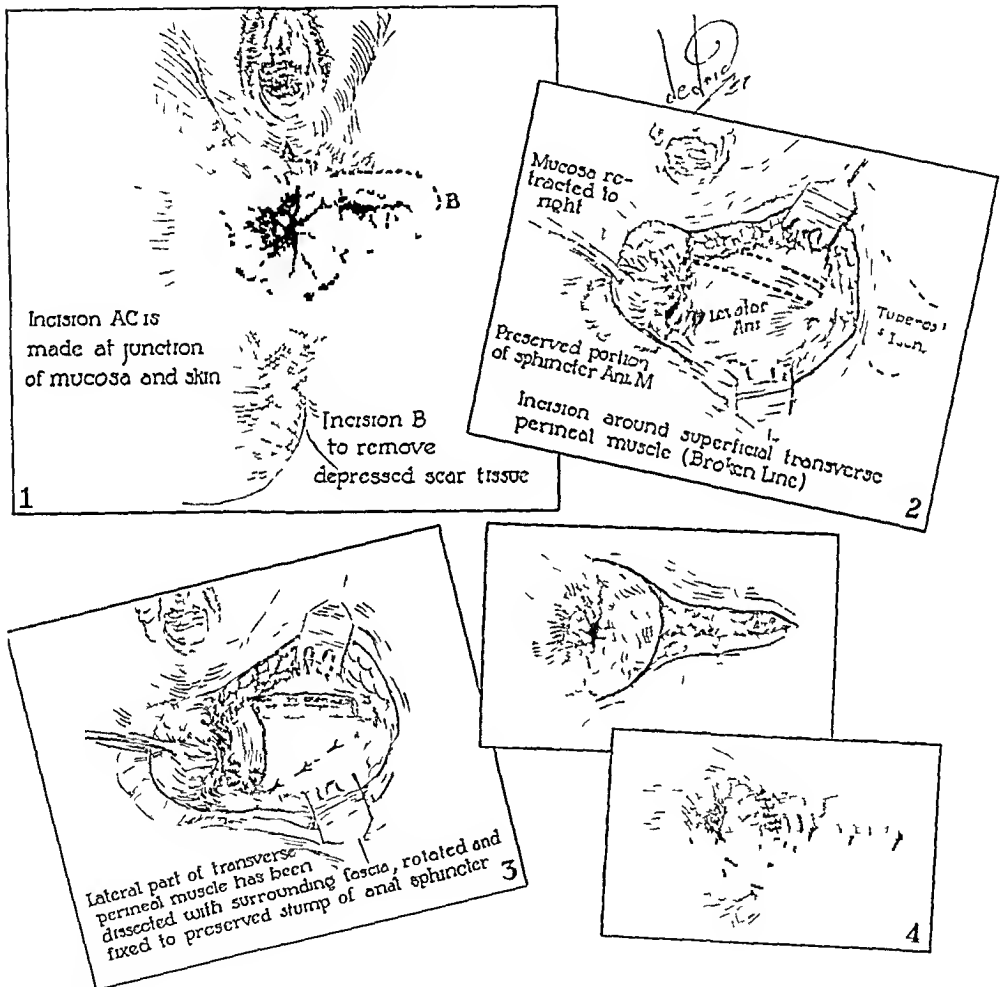
Reconstruction of voluntary control has given us great encouragement during the last eight years. In 1929, Wreden<sup>8</sup> reported the employment of fascia from the gluteus maximus muscle threaded through two vertical incisions lateral to the anus, encircling it by a strip from each side. Harvey Stone<sup>9 10 11</sup> employed the preserved fascia of Koontz as a subcutaneous purse string suture about the anal canal, introduced through two small incisions at the anterior and posterior commissures. The incisions were connected with each other by subcutaneous blunt dissection. Strips of fascia were threaded through the tunnels thus formed, drawn up and fastened to the gluteus maximus muscle.

Before presenting the following case a brief review of the anatomy involved would help clarify the procedure.

*Anatomic Considerations*—The transverse perineal superficialis muscle is a narrow slip of muscle passing transversely across the perineal space in front of the anus. It arises from tendinous fibers from the inner and foremost part of the tuberosity of the ischium and is inserted into the central tendinous point, joining with the muscle of the opposite side, with the external sphincter ani behind, and the bulbocavernosus in front. Some of the deeper fibers

of the external sphincter and decussate in front of the anus and are continuous with the transverse perineal superficialis. The action is to fix the central tendinous point, its nerve supply is by the perineal branch of the pudendal nerve. The external sphincter is supplied by the 4th sacral and branches from the inferior hemorrhoidal branch of the pudendal nerves.

The fascia involved is the superficial, which is composed of a superficial and deep layer. The superficial layer is a thick but loose areolar tissue in



(1) Incisions shown by dotted line (2) Location of superficial transverse perineal muscle (3) Method of transplant (4) Final closure

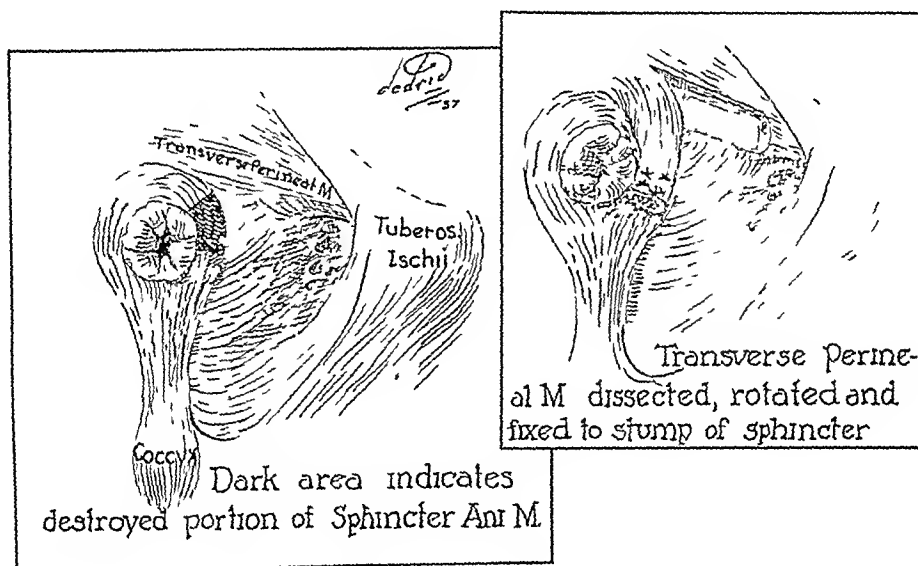
texture, which is continuous in front with the dartos tunic of the scrotum, behind to the subcutaneous tissue of the anus, and at the sides with the fascia of the thigh. The deep portion (Colles) is a thin aponeurotic structure of great strength which binds down the root of the penis muscles. In front it is continuous with the deep fascia of the penis, spermatic cord and Scarpa's fascia of the abdominal wall, at the sides it is attached to the margins of

the ram of the pubis and ischium. Posteriorly, it curves around the transverse perineal superficialis to join the inferior fascia of the urogenital diaphragm. The strength of the transverse perineal superficialis is greatly enhanced by this fascia.

**Case Report**—C Z, colored, female, age 29, married, was admitted May 4, 1937. Previous admissions: February 29, 1936, to the Gynecologic Service with a right Bartholin cyst and rectal fistula. On March 6, 1936, electrocoagulation of the Bartholin cyst and fistulectomy was performed. Uneventful recovery, discharged March 14, 1936, to the Out-Patient Department. Second admission, March 15, 1936, postoperative bleeding from fistulectomy incision. The bleeding was easily controlled by an adrenalin pack. She was discharged March 20, 1936, to the Out-Patient Department.

**Subsequent Course**—Result of previous operation unsuccessful, causing patient to be incontinent of both gas and feces, so much so that it was necessary for her to wear a cloth in order to prevent expelling even a constipated stool, also complained of a bulging, ring-like mass which could be held up only by padding.

**Physical Examination**—This was essentially negative other than that which per-



Detail of the muscle damage and its repair

tained to the rectal pathology. The rectum presented a large ring of prolapsed mucosa, also a wide, depressed scar in the left anterior quadrant. Digital examination revealed no masses or tender areas, but a markedly relaxed anus which easily admitted all the fingers of the hand. **Diagnosis**: Postoperative anal incontinence.

**Operation**—May 6, 1937. Under spinal anesthesia of 100 mg of spinocaine, a curved incision was made following the mucocutaneous junction, extending from the central tendinous point to the level of the anococcygeal raphe. An incision circling the previous operative sight, surrounding the scar, was extended from the first incision (Fig 1). The mucosa was freed and retracted toward the opposite side. The old scar was dissected out and removed, leaving normal soft tissue. The skin flaps were dissected anteriorly toward the perineum and posteriorly toward the anococcygeal raphe (Fig 2). The transverse perineal superficialis with its surrounding fascia was exposed, the muscle was freed from its outer border near the tuberosity of the ischium to the central tendinous

point The muscle was then transplanted, surrounding the left side of the anus, and carefully sutured to the remains of the old sphincter, one-half inch lateral to the midline posterior, with 20 day chromic catgut Deep sutures were inserted to the levator for anchorage (Fig 3) The fascia was sutured to give added support, and the soft tissues were also drawn together to afford still more support The skin was closed with dermal sutures and the mucosa was replaced over the new sphincter and connected to the skin margin (Fig 4)

A slight rise in temperature and pulse occurred during the first night but was normal thereafter

As a result of infection the skin sutures pulled out and allowed separation of the wound The deep structures, however, remained intact The bowels were opened one week later and daily thereafter She was discharged on the eighteenth postoperative day, with a slight separation of the skin margins but with complete control of her bowels, and felt perfectly comfortable She returned to the Out-Patient Department for dressings When discharged from the Out-Patient Department three months later, she wore no dressings, had no leakage, and had complete control of her bowels

#### SUMMARY

- 1 A case of postoperative anal incontinence is reported in which a cure resulted from the procedure detailed
- 2 The transverse perineal superficialis, with its deep layer of the superficial fascia, functioned successfully as a voluntary sphincter
- 3 Anatomically it proved convenient for this type of repair
- 4 It is necessarily limited in its field of usefulness

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## HYPERTROPHY OF THE SPIRAL MUSCLE OF THE RENAL PAPILLA

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CONTRACTIONS of the renal pelvis have been observed during physiologic experimental research work upon the cat and dog. They are described as rhythmic but fleeting in character. Powerful contractions have never been seen. Wassink<sup>4</sup> reports contractions observed on the cat which probably were contractions of the ureter, since the cat's pelvis is entirely intrarenal. He also reports having observed such contractions in the pelvis of the human kidney after its removal.

We observed very powerful contractions of a large, extrarenal human pelvis, in situ, on the operating table, which appeared every 15 to 20 seconds and lasted five seconds at a time. The pelvis, measuring about 5x5 cm, would contract and entirely disappear within the hilus of the kidney (Fig 1), remain there five seconds, then expand to its previous size during the stage of relaxation. We saw systole and diastole at regular intervals without interruption.

**Case Report**—Hosp No 94610, referred by Dr Charles Kutner M G, white female, age 42, was admitted to the Mt Sinai Hospital, September 9 1935, complaining of pain in the right loin. The illness had begun four months previously with attacks of pain in the left loin, which came on suddenly, starting in the loin and radiating down to the pubes and were of sufficient severity to necessitate the administration of morphia. Roentgenologic examination revealed a small shadow in the lower end of the left ureter. After several cystoscopic manipulations at another hospital, an indwelling catheter was placed up to the left kidney. While the catheter was in situ the patient began experiencing pain in the right loin. The stone was passed spontaneously after two weeks. While the pain in the left loin subsided with the passage of the stone, that in the right loin persisted. From now on, the attacks of pain in the right loin appeared frequently and were of the same character, radiation and severity as those she had experienced previously on the left side. During an episode the seizures occurred regularly at one minute intervals, and were accompanied by nausea and vomiting. Following each attack the patient was unable to void for from three to five hours. There was no frequency, dysuria or hematuria during the free intervals.

*Previous History*—Pneumonia 17 years ago. Right oophorectomy and appendicectomy in 1926. Cholecystectomy in 1929. Menses began at 16, painful, duration four days. Married 23 years. Had had three pregnancies and one miscarriage. Children living and well.

*Physical Examination* was essentially negative except for abdominal scars and some tenderness in both flanks, particularly on the right side. Kidneys not palpable. T P R normal. *Objective Findings*—Roentgenologic. Gastro-intestinal tract negative. Biliary tract negative. Intravenous urography. Normal except for some dilatation of the pelvis of the right kidney. Sigmoidoscopy. Atrophic sigmoiditis. Neurologic examina-



tion Negative Teeth Three infected teeth with inflamed gums *Laboratory Data*—Urine Acid, 1016, albumin trace, WBC 3-4, RBC none Blood RBC 4,340,000, Hb 83 per cent, WBC 7,200, polys 62 per cent Blood chemistry BUN 17.9, sugar 87 Wassermann and Kahn Negative Basal metabolism -7

*Cystoscopy*—September 27, 1935 The patient was cystoscoped during a mild attack of right loin pain Bladder normal Catheter passed up to the right kidney without obstruction Twenty cubic centimeters of clear urine were found retained in right renal pelvis After emptying the renal pelvis, all pain in the loin disappeared *Diagnosis* Adynamic hydronephrosis

*Operation*—October 2, 1935 Under spinal anesthesia the right kidney was exposed It was found to be small and unrotated The pelvis was fairly large and entirely extra-

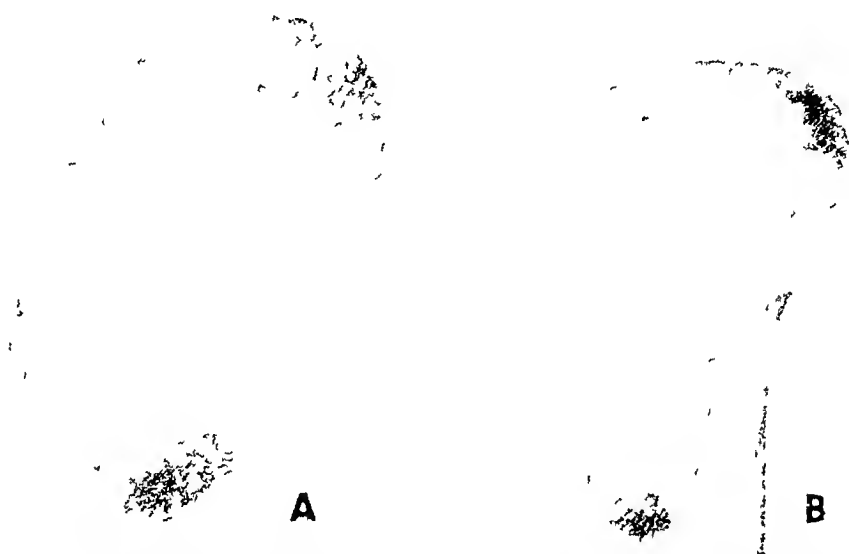


FIG 1—Drawing showing contraction of the renal pelvis which occurred every 15 to 20 seconds as observed at operation October 2, 1935 (A) Before contraction (B) After contraction

*Operative Procedure* Nephro and ureterolysis and sympathectomy

renal On observing the kidney an unusual condition was noted every 15 to 20 seconds there was a contraction of the renal pelvis and complete disappearance of the extrarenal pelvis within the hilus of the kidney After about three to five seconds the entire pelvis would relax and emerge in its entirety from the hilus of the kidney (Fig 1) These contractions promptly stopped after incision of the pelvis No obstruction was found at the ureteropelvic junction Complete nephrolysis, ureterolysis of the upper third of the ureter, and sympathectomy were performed The pelvis was resutured without return of the contractions

Convalescence was uneventful, and the patient was discharged 14 days postoperative, October 17, 1935 free from pain

*Subsequent Course*—Readmission to hospital February 19, 1937, No 105627 The patient had felt well and was free from pain for only a short period after discharge from the hospital She now had continuous, rather than intermittent pain in the right loin, which became worse on standing She had had numerous injections of alcohol into the intercostal nerves without avail In November, 1936, a complete section of the ninth to the twelfth intercostal nerve was performed without relief

Physical examination revealed nothing unusual, condition same as two years before

The urine was clear, containing only six to eight WBC and a faint trace of albumin. Blood count and chemistry were normal.

*Second Operation*—Because of persisting pain a right nephrectomy (Fig 2) was performed. At operation the kidney proper was found unchanged, the pelvis, however, had become much larger, and the wall much thinner, but no contractions could be observed at this time. Convalescence was again uneventful, and the patient was discharged 14 days postoperative, in excellent condition.

*Histologic Examination*—Dr D Meranze. The removed kidney showed nothing unusual but on studying the area of the papillae we noted massive hypertrophy of the spiral muscle, a condition which was described in 1926 (Muschat<sup>1,2,3</sup>). Instead of strands of muscle fibers, one found heavy bundles of hypertrophied musculature, especially well demonstrable by the Mallory stain (Figs 3 and 4).

Second readmission to hospital February 1, 1938, No A—2677. The patient stated that she had had very little, if any, relief from pain in the right loin since the nephrectomy one year previously. There was an almost constant, gnawing, dull pain in the right loin, which varied in intensity at different times. In addition there had occurred spasms of sudden sharp pain in the left loin, which, as had been noted in 1935, began posteriorly in the costovertebral angle and spread anteriorly in a hemigirdle fashion. Now, however, the pain in the left loin had become associated with an increase in the frequency of micturition and some dysuria.

*Physical Examination*—No abnormality found. No loin tenderness was elicited at this time. Intravenous urography revealed a large left kidney due to physiologic, compensatory hypertrophy which showed normal renal architecture. The urine was clear, with two to three WBC. Blood count and chemistry were normal. Cystometrogram. First desire to void at 300 cc. Pressure curve low and maximal voluntary pressure only 25 to 30 Mm Hg. Neurologic examination. No evidence of organic neurologic disease. Possibility of ailment being functional, conversion hysteria. *Diagnosis*. Early neurogenic bladder of hypotonic type. Patient discharged to return for further neurological study.

*Comment*—The cause of the adynamic hydronephrosis cannot be stated. Neither is there evidence to explain the unique hypertrophy of the spiral muscle of the papillae. Both conditions must be designated as idiopathic until more is known about them. One may theorize upon the cause and effect in this case. If the hypertrophy of the renal musculature is primary,

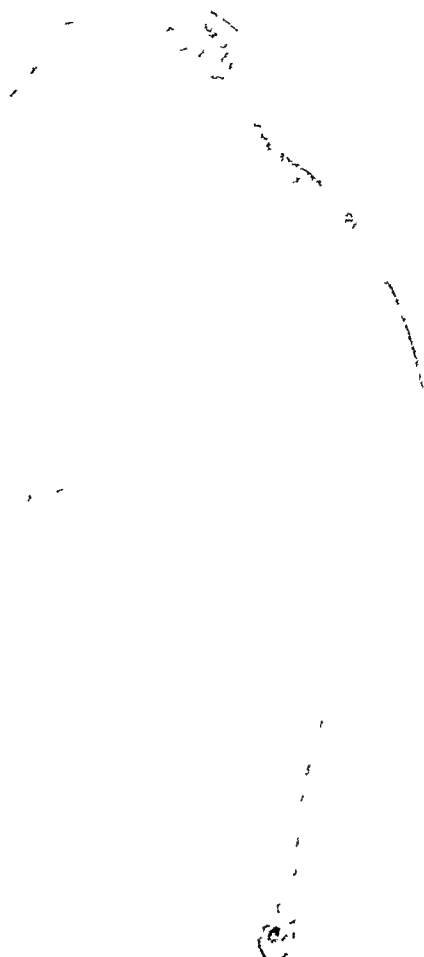


FIG 2—Drawing showing the degree of progressive dilatation of pelvis as found at operation in February, 1937.  
*Operative Procedure*. Nephrectomy.

it can explain the symptomatology observed, namely, the rhythmic, painful contractions "like a clock" complained of by the patient. Every contraction

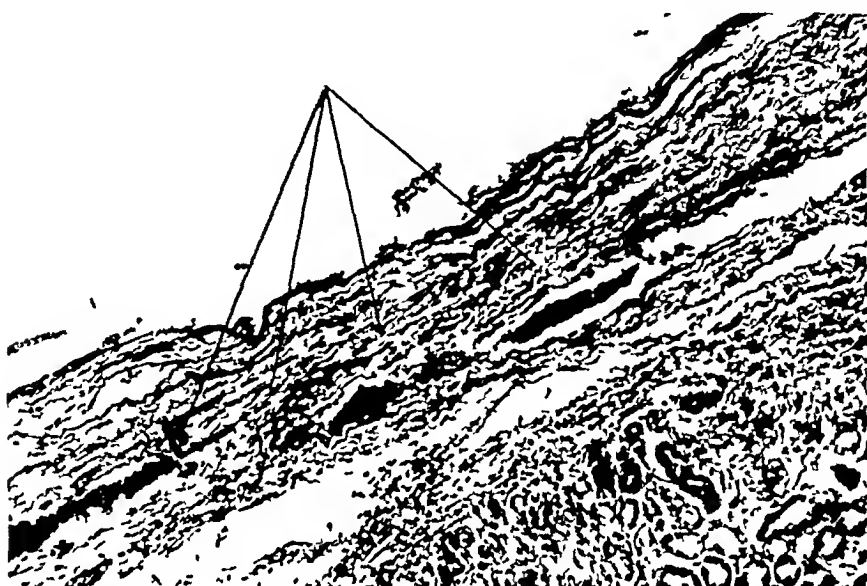


FIG 3.—Photomicrograph of the wall of a calyx showing the normal appearance of the spiral papillary muscle. The muscular fibers are thin and small.

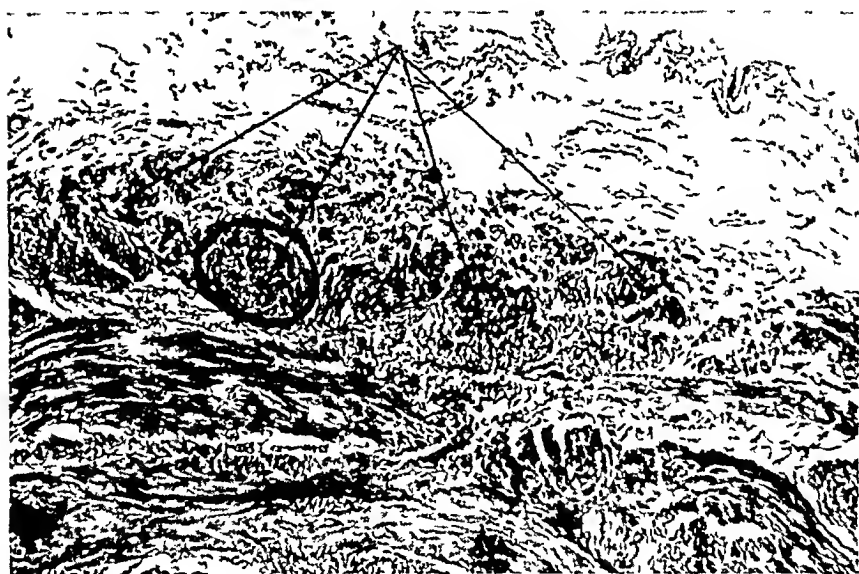


FIG 4.—Photomicrograph of the wall of a calyx in the kidney removed from the case herewith presented. Note the many thick bundles of the spiral papillary muscle.

would produce the tetanic, painful spasm of the pelvis lasting five seconds which was so plainly demonstrable on the operating table.

Another symptom complained of appears to be of great physiologic importance, namely, the complete anuria for from three to five hours following the attacks of renal spasm. Is it possible that during such attacks there was a

continuous tetanic contraction of the spiral muscles of the papillae, thus cutting off the urinary flow from the kidney for a long period of time? Is it the lack of regular contractions of the papillary muscles during this period, the lack of the milking effect upon the papillae, that caused this temporary anuria noted regularly during these attacks? The possibility that the hypertrophy of the papillary muscles is due to obstruction cannot be maintained. Careful studies of this muscle in many cases of renal obstruction showed no evidence of hypertrophy. Two cases of stone in the ureter were studied, one case of congenital valve formation of the posterior urethra and two cases of prostatic hypertrophy. In all these five cases, there was much evidence of acute and chronic renal obstruction, yet in none of them were we able to find the muscle hypertrophied to any demonstrable degree. We must, therefore, dismiss the theory of the secondary hypertrophy of the papillary muscles because of obstruction.

#### SUMMARY

(1) A case of adynamic hydronephrosis, necessitating nephrectomy, is described.

(2) Powerful rhythmic contractions of the renal pelvis were observed at length on the operating table.

(3) Massive hypertrophy of the spiral muscles of the renal papillae was found.

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## FIBROMYOMA OF THE OMENTUM

W. KENNETH JENNINGS, M.D.

EVANSTON, ILL.

FIBROMYOMA occurring independently in the omentum is rarely encountered. The literature affords records of but seven instances of this unusual condition. In 1912, two cases were reported by Loewert<sup>1</sup> and Boerner,<sup>2</sup> respectively. Joachimovitz<sup>3</sup> described a case of malignant myoma of the omentum, in 1930. In the same year Schleyer<sup>4</sup> and Uhle<sup>5</sup> each recorded cases of benign fibromyoma of the omentum. Bazterrica's<sup>6</sup> case, reported in 1931, and that of Martin,<sup>7</sup> in 1933, conclude the series to date.

In most of the cases reported associated fibromyomata of the uterus were noted. Joachimovitz's patient had been subjected to a supravaginal hysterectomy for fibroids 20 years previously. Such findings, together with the marked similarity in histologic structure between these omental myomata and those which occur so frequently in the uterus, have influenced Uhle, Curtis,<sup>8</sup> and others to postulate that such tumors originate as subserous uterine fibroids which later become enveloped by the omentum, receive a collateral circulation from the latter organ, and ultimately are detached from the original host. In two of these cases the tumor was attached to the omentum by a cord-like structure which was highly vascularized. Uhle's patient manifested symptoms of peritonitis, and a preoperative diagnosis of ovarian cyst with a twisted pedicle was made. At operation it was discovered that a torsion of the pedicle had compromised the blood supply of the myoma.

All such tumors should be readily palpable under normal conditions. In the writer's case, however, as in that of Uhle, peritonitis with its resultant reflex spasticity of the abdominal muscles rendered palpation very difficult. Lipomata of the omentum and true cysts of the mesentery might easily be confused with omental myomata. The demonstration of a freely movable tumor situated in the region of the epigastrium in a patient with palpable uterine fibroids should suggest the possibility of the presence of one of these late neoplasms.

**Case Report**—Hosp No 513 B C, colored, married, age 30, was admitted to the Evanston Community Hospital January 19, 1937, complaining of severe pain in the abdomen which had begun 24 hours previously and was at first situated in the lower quadrant, but which, after several hours, became more diffuse, eventually becoming general. However, at the time of examination the patient complained of predominant distress in the right abdomen just lateral to the umbilicus. There had been associated nausea, vomiting (which the patient stated was self-induced) had occurred once. Several similar but less severe attacks had been experienced during the past two years. A vaginal discharge was admitted. Patient had never been pregnant. There was nothing abnormal about the menstrual history.

*Physical Examination* revealed a generalized rigidity of the abdomen. Tenderness appeared most pronounced on the right side. Pelvic examination disclosed the uterus enlarged to the size of a five months' pregnancy, its irregular surface indicated the presence of fibromyomata. Manipulation of the cervix and fundus caused pain. White blood cells 16,000. Urine, essentially normal. Temperature, 100.2° F. Weight, 180 pounds. A diagnosis was made of peritonitis due either to torsion of a pedunculated, subserous fibroid or to a cystic ovary with a twisted pedicle. The possibility of perforated appendicitis was entertained.

*Operation*—January 19, 1937. Under ether anesthesia, the abdomen was opened through a low midline incision. It contained a moderate amount of serosanguineous fluid. The uterus contained a number of large fibroid tumors, several of which were subserous. The ovaries were twice their normal size and contained multiple small cysts. Both fallopian tubes were edematous and appeared chronically inflamed. A subtotal hysterectomy was performed.

The appendiceal area was explored. To the left of the cecum, a structure was encountered which felt very much like an umbilical cord, this was followed to the lower epigastrium where its attachment to a rounded, semisolid tumor, the size of a

## FIBROMYOMA OF OMENTUM

grapefruit, was discovered. At its other end the cord was found to be continuous with a short omentum. Owing to the high attachment of this pedicle, the original incision was closed and a right paramedian incision made just above the level of the umbilicus. Through this opening the omental fibroid was delivered, its cyanotic appearance together with its many engorged blood vessels suggested strangulation of its pedicle. Ligation and section of the base of the pedicle were carried out and the tumor removed (Fig 1). The incision was then closed in layers without drainage.

*Pathologic Examination*—Gross (Dr E L Benjamin) "The specimen consists of a solid, somewhat oval tumor mass measuring  $15 \times 10 \times 8$  cm, and weighing 576 grams. The external surface is composed of a glistening, gray-pink capsule well supplied with numerous blood vessels. Projecting from the external surface are knob-like promi-

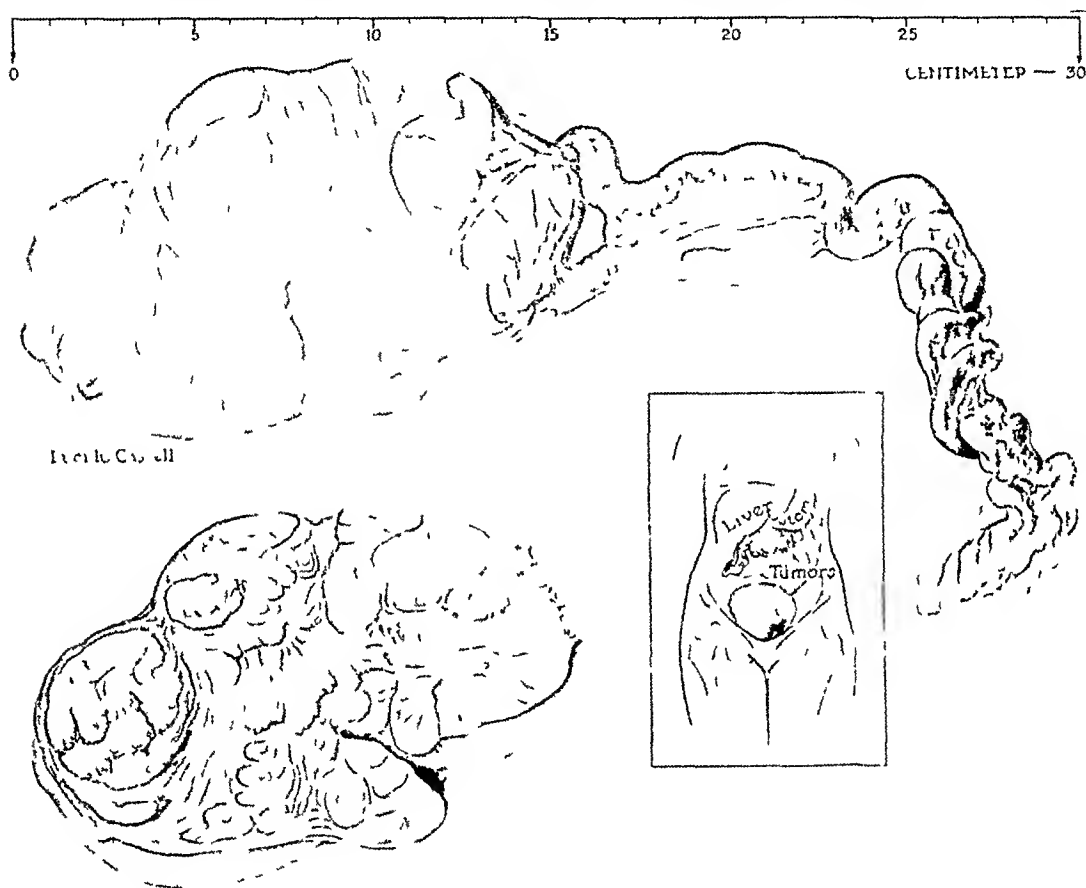


FIG 1—Fibromyoma of omentum with cord like pedicle. Inset shows relationship to other abdominal organs.

nences, seven in number, the largest of which is 6 cm broad and elevated to a height of 3 cm. Attached to one extremity of this tumor mass is a pedicle 21 cm long and 7 cm in diameter. This is composed of atrophic, twisted omentum which incorporates engorged and thrombosed veins, which are twisted in a corkscrew manner about the omentum. The largest diameter of these veins is 8 mm. The pedicle also incorporates a tortuous cord resembling somewhat an umbilical cord which is composed of material resembling subserous atrophy of fat tissue. Bisection of the tumor mass reveals it to be composed of masses of interlacing gray-pinked whorls, and firm tissue interspersed with linear markings of a darker gray and somewhat softer tissue. The pole opposite the attachment of the pedicle contains a 4.8 cm, round, well demarcated, soft, white, degenerating tumor mass." *Microscopic Diagnosis*—Path No 148 (1937) Fibroleiomyoma with anemic infarction. Thrombosis of veins of the pedicle with serous atrophy of mesenteric fat tissue.

*Gross Description of Excised Uterus*—The uterus was enlarged to the approximate size of a five months' pregnancy and was found to contain five typical subserous fibroid tumors ranging in size from that of a marble to an orange. One of the smaller of these tumors was attached to the fundus of the uterus by a short pedicle measuring  $1\frac{1}{2}$  cm in length and  $\frac{1}{4}$  cm in diameter. On section it was seen that the walls of the uterus were essentially replaced with tissue typical of leiomyofibroma.

The patient was discharged from the hospital on the eleventh postoperative day. Her subsequent recovery was complete, both wounds healing per primam.

#### SUMMARY

A case is reported of an omental fibromyoma whose pedicle had undergone torsion with resultant compromise of the blood supply of the tumor. The clinical picture was that of diffuse peritonitis which, together with an enlarged fibroid uterus, provided the only diagnostic criteria.

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## BOOK REVIEW

THORACIC SURGERY By Ferdinand Sauerbach, M D , and Laurence O'Shaughnessy, M D , F R C S Philadelphia J B Lippincott Co , 1938

One cannot read this book without being impressed by the tremendous experience from which it has been the good fortune of the authors to draw. Every subject that they discuss is well supported by ample case reports. This is particularly well demonstrated in the chapters on severe injuries to the chest, and the war experiences of the authors in handling such serious problems are very fertile. The illustrations are well chosen and often the mechanics of obscure clinical pictures are lucidly demonstrated by these illustrations and diagrams.

The importance of positive pressure anesthesia in this branch of surgery is correctly emphasized. However, in evaluating the various gases, one notes that cyclopropane is not mentioned. I believe enough experience has been gained with this gas, using a high oxygen mixture, to feel that it is a valuable surgical aid.

In the chapter dealing with ischemia of the heart, two main schools of thought at present exist, one headed by author, Laurence O'Shaughnessy, who feels that omentopexy represents the most efficient means of reestablishing a new circulation to the myocardium, and the other school headed by Beck. Both, of course, support the same fundamental principle—the importance of establishing a new blood supply—but the latter feels that the pectoral muscle transplant is a more satisfactory method. The experience of the reviewer in this work would lead him to believe that the authors have given too little attention to the clinical-experimental work of Beck and his associates. This is lamentable, in view of the fine animal experiments they have performed to logically justify their opinion.

Again the value of a hyperoxygenated blood, which cyclopropane very helpfully produces, is not mentioned, nor is any note made of the value of the defibrillator in bringing the heart out of ventricular fibrillation. If such a tragedy should develop during the operation, in view of its life-saving importance, this instrument should be always available. In these same cases the importance of rest periods has been correctly emphasized.

Although now recognized only for its historic value in surgical development, it is hard to account for the failure to make any mention of the negative pressure chamber of Willy Meyer, particularly as extensive credit is given to Continental workers.

The chapter dealing with "The Control of an Open Pneumothorax" tersely sums up most of the principles of positive pressure anesthesia with which all surgeons and anesthesiologists should be conversant if performing any thoracic surgery. The discussion of the dynamics of fluid in the pleural sac



and of tension pneumothorax, with the accompanying diagrams, simplifies the clinical pictures that one often sees where these dynamic alterations have progressed to involve the heart and great vessels in the mediastinum. When this compression is marked, the accompanying referred abdominal symptoms are very easily appreciated. A faulty understanding of this mechanism in some cases has been responsible for unnecessary celiotomy.

In view of the recent developments in this field, many interesting advances in thoracic physiology, not commonly known or understood, are very clearly presented. Several old misunderstandings regarding thoracic function are cleared up in that section of the book dealing with diaphragmatic physiology. The following is a good illustration in point: "The diaphragm plays no active part in the act of coughing and indeed in certain diseases, such as basal bronchiectasis, induced paralysis of the diaphragm assists expectoration."

I believe this book can be read with great profit by all physicians actively engaged in surgical practice. The general practitioner or internist will find many clearly presented problems to which modern surgery can give a good prognosis in otherwise hopelessly doomed cases, and the excellent bibliography will further incite his interest.

EDWIN J. GRACE

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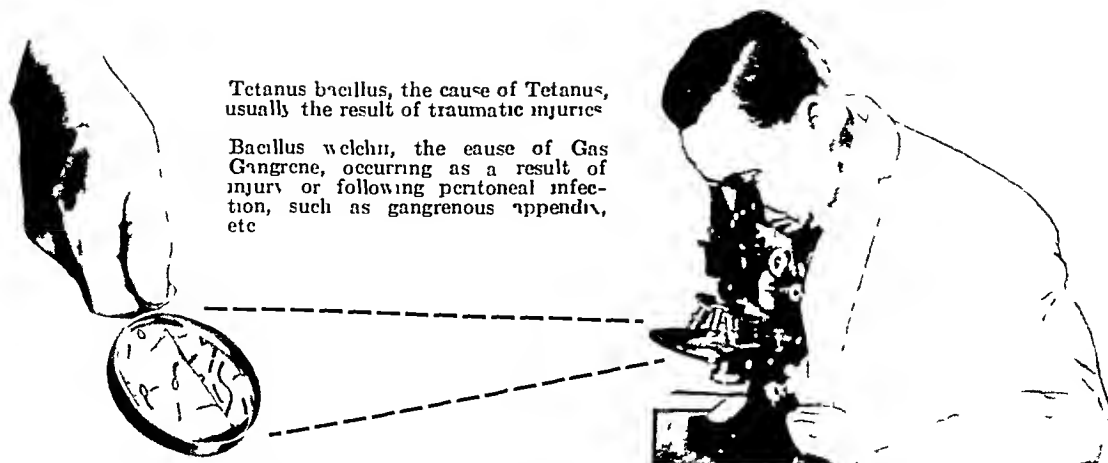
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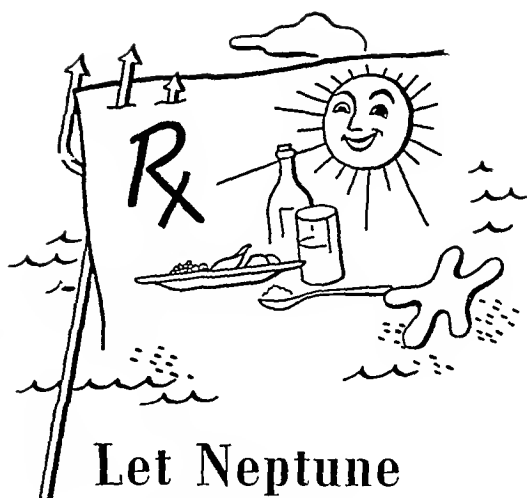
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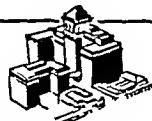
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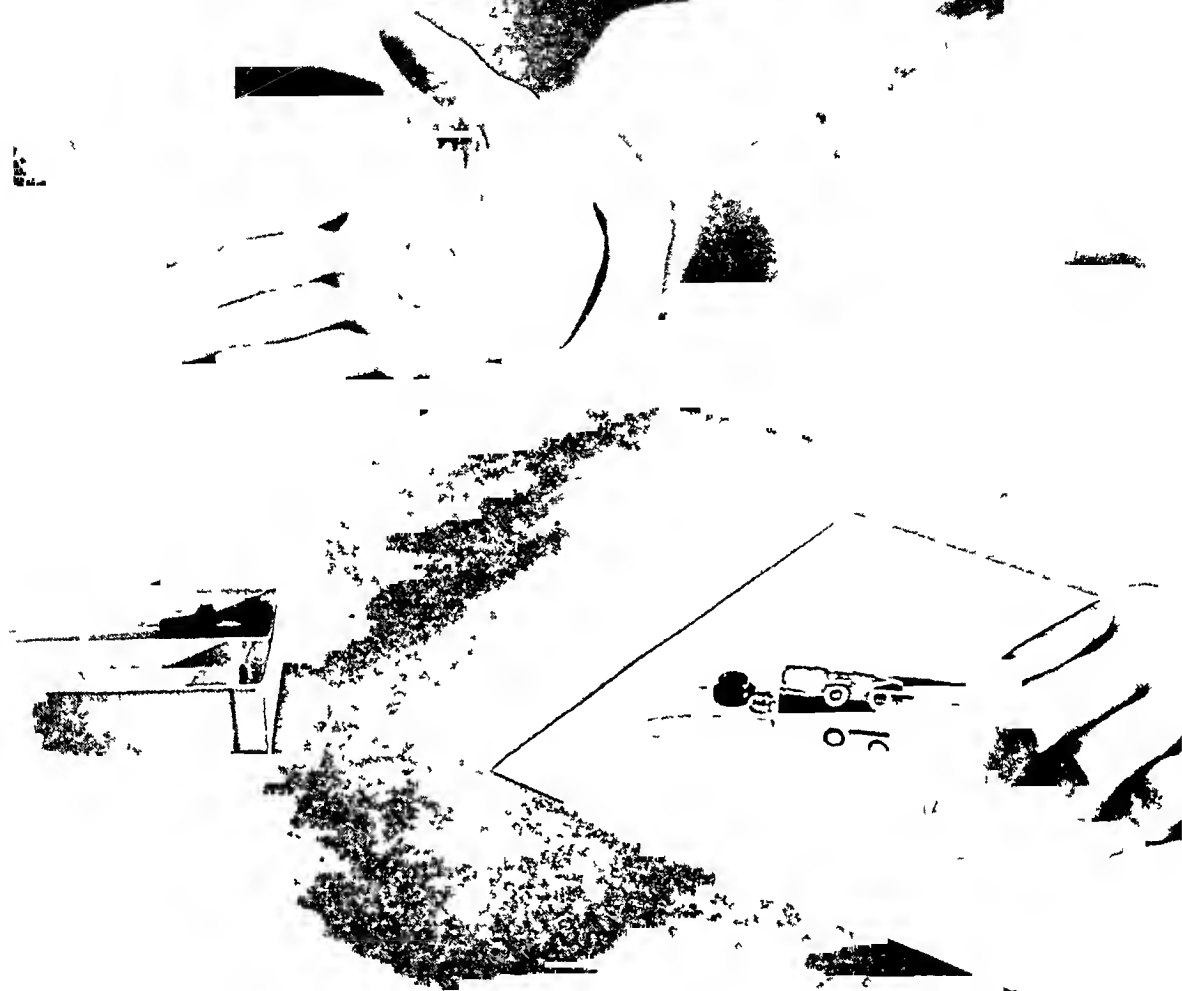
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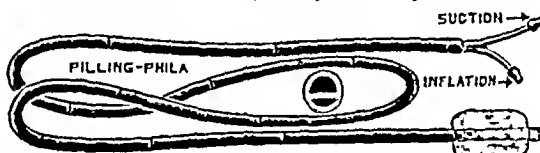


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(See American Journal of Medical Sciences 187 595 1934 and  
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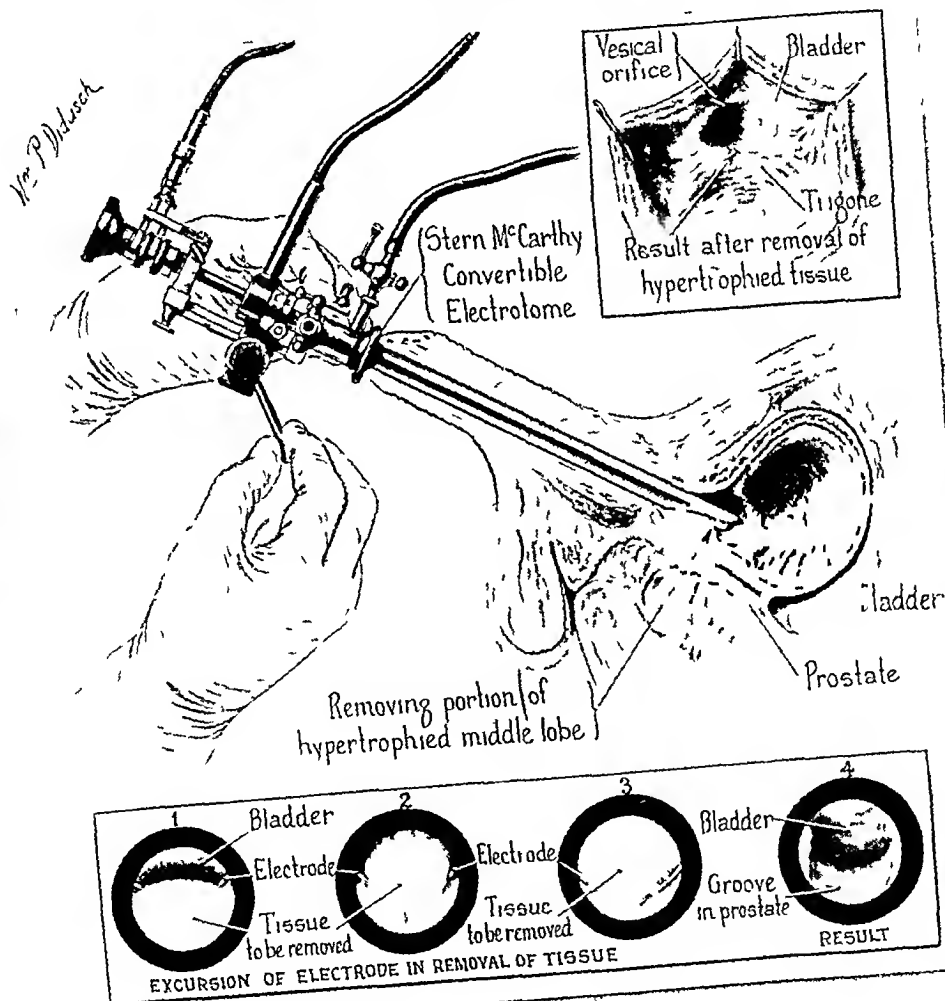
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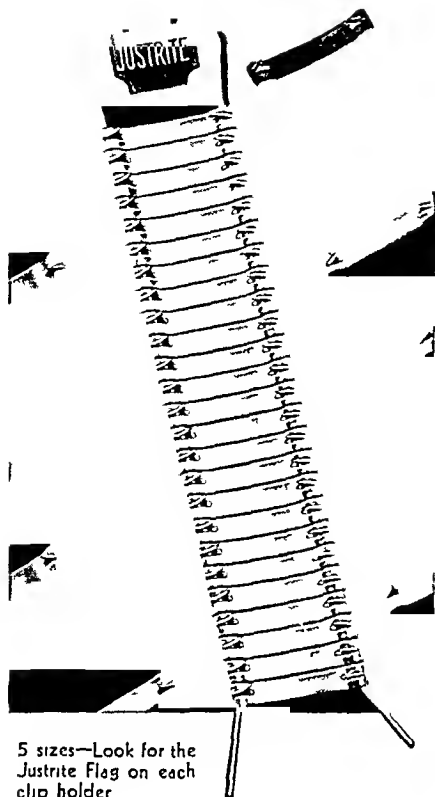
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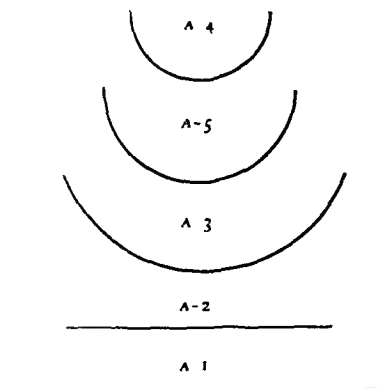
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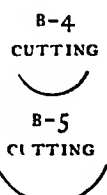
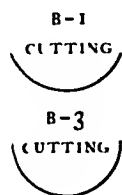
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1663	Plain Catgut	4-0	B-5
1665	Black Silk	6-0	B-1
1665	Black Silk	4-0	B-1
1667	Plain Catgut	3-0	B-4
1669	10-Day Catgut	4-0	B-5
1669	10-Day Catgut	3-0	B-5
1669D	10-Day Catgut †	4-0	B-5
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1664	Black Silk *	6-0	B-1
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1666	Plain Catgut *	3-0	B-4
1668	10-Day Catgut *	4-0	B-5
1668	10-Day Catgut *	3-0	B-5
1668D	10-Day Catgut †	4-0	B-5
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1752	Aluminum-Bronze Wire	00	C-1
1753	Black Braided Silk	000	C-2
1754	Aluminum-Bronze Wire	00	C-4
1755	Kal-dermic	00	C-3
1758	Aluminum-Bronze Wire	00	C-3

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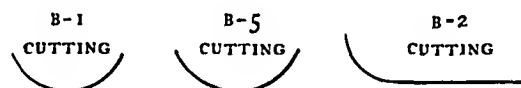
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1651	Kal-dermic	6-0	B-1
1652	Kal-dermic	8-0	B-5
1652	Kal-dermic	6-0	B-5
1652	Kal-dermic	4-0	B-5
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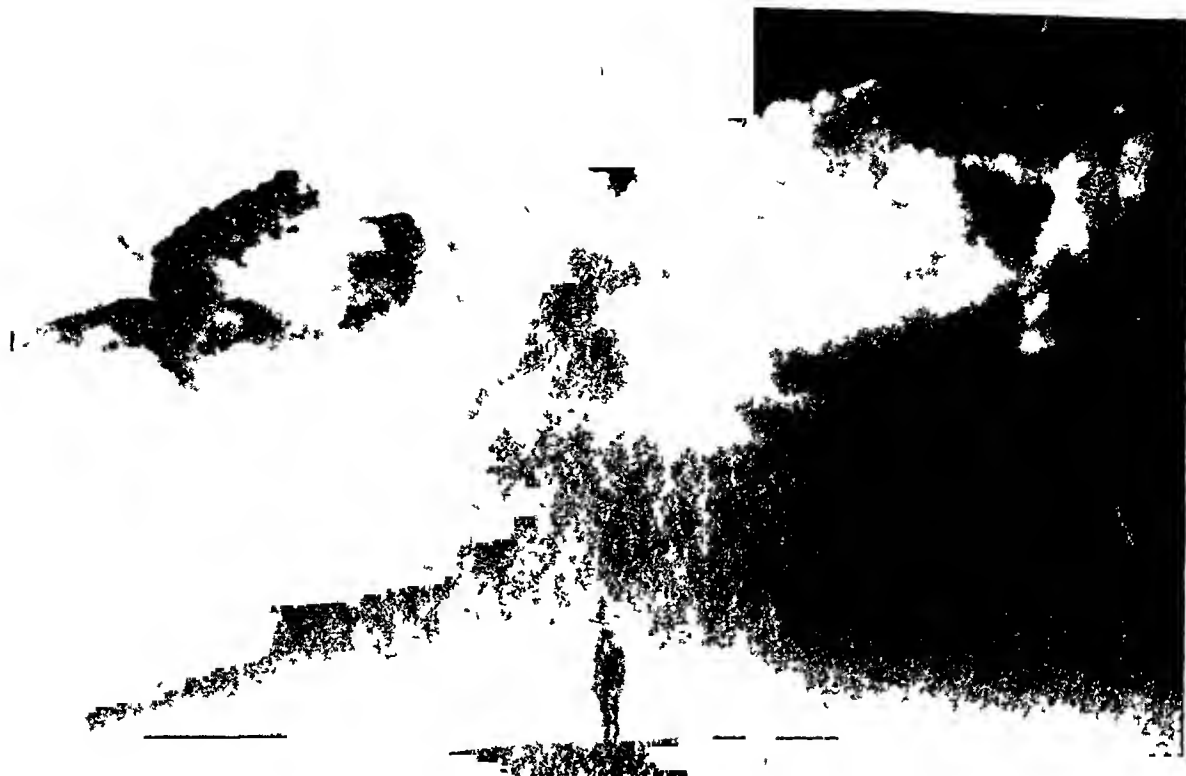
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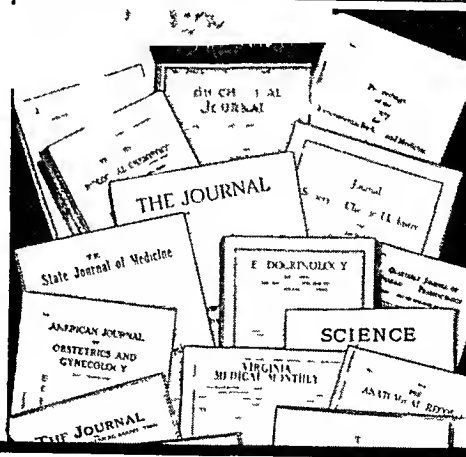
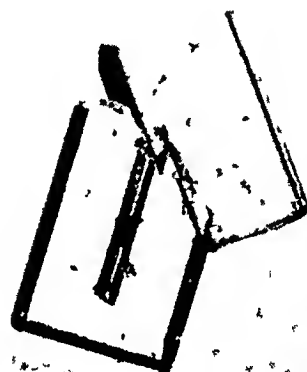
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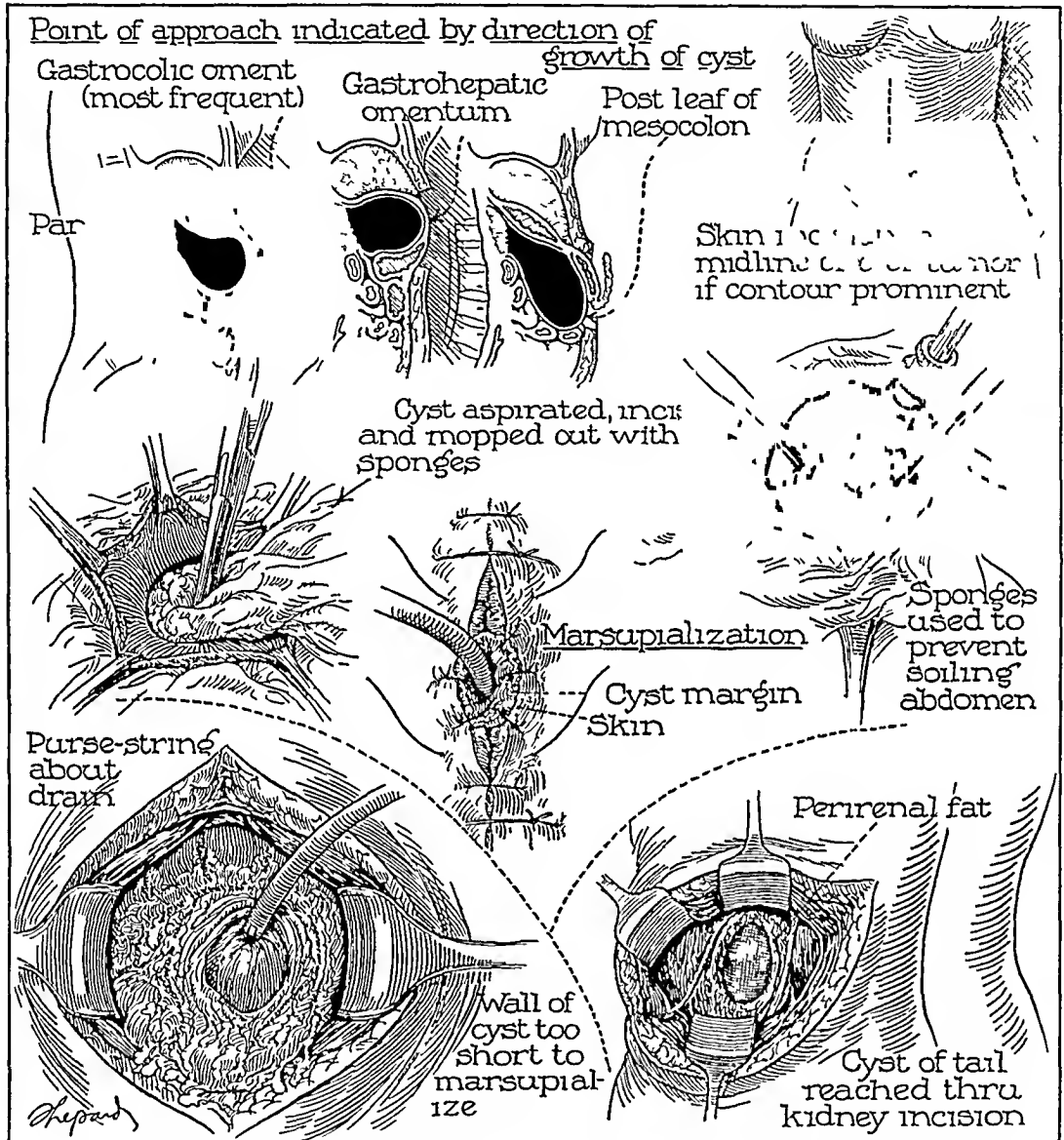
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## VARIATION IN THE CHOLESTEROL, BILE PIGMENT AND CALCIUM SALTS CONTENTS OF GALLSTONES FORMED IN GALLBLADDER AND IN BILE DUCTS WITH THE DEGREE OF ASSOCIATED OBSTRUCTION \*

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THE fundamental cause of gallstone formation is still very little understood despite the amount of study which has been devoted to the physiology and chemistry of the bile, the composition of the stones, and the associated pathology and bacteriology of the biliary tract. Stones may form either in the gallbladder or in the bile ducts, and both sites have to be considered in determining the rôle which any factor may play in determining their chemical composition. This fact is often lost sight of and proportionately much more attention has been paid to stone formation in the gallbladder than to that in the bile ducts. Some of the factors that have been considered, or are known to influence stone formation, are obstruction, infection, reflux of pancreatic juice or duodenal contents, altered cholesterol metabolism with increased output of cholesterol in the bile, increased bile pigment output in hemolytic icterus, reduction in the ratio between nonsaponifiable substances (cholesterol) and saponifiable substances (fats and fatty acids) in the bile, dyskinesia, and over-concentration of the salts of the bile acids with resultant injury to the gallbladder wall. Of these, the one whose rôle is most clearly established, although it may not be of fundamental importance, is obstruction.

Clinical and operative studies have been made of cases of cholelithiasis and traumatic strictures of the ducts, and chemical analyses, radiograms, and roentgenographic powder diagrams have been made of stones removed from such gallbladders and common and hepatic ducts, in an endeavor to throw light on their chemical composition as influenced by the site of stone formation and by any coexisting obstruction, also on the source of the chemicals themselves, whether they are derived from the bile or from the wall of the gallbladder.

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\* This work was done in part on a grant from the Douglas-Smith Foundation for Medical Research. Submitted for publication September 9, 1938.

**CHEMICAL METHODS**—Cholesterol was determined by the method of Bloo<sup>1</sup>, Pelkan and Allen<sup>1</sup> for blood cholesterol applied to an ether extract of the stones. Calcium was determined by the method of Clark and Collip,<sup>2</sup> and phosphorus by the method of Phiske and Subbarow.<sup>3</sup> Bile pigments were determined by a method introduced by one of us (H G A<sup>4</sup>) as follows. The stones were extracted with a mixture of equal parts of chloroform, alcohol and glacial acetic acid. The extract was refluxed and then oxydized to a blue end-point with perchloric acid. Standard bilirubin solution was used for comparison.

**PHYSICAL METHOD**—Roentgenographic powder diagrams were made of the stones in the following way. The material, first unpowdered and then powdered, was placed in a Pyrex tube which in turn was placed in a cylindrical powder camera and radiated by roentgen rays (copper K alpha) for ten hours. The resulting lines on the exposed films serve to identify the materials. This analysis is capable of indicating not only certain chemical compounds but also the specific crystalline forms in which they may be present. Detailed reports of the analyses are given in a separate publication by one of us (R P<sup>5</sup>).

*Stones Formed in the Gallbladder*—The chief building materials of stones in the gallbladder are cholesterol, bile pigments and calcium compounds, predominantly calcium carbonate, but in two cases the compound of tricalcium phosphate and calcium carbonate, resembling dahlite, was present. The materials become enmeshed in a colloidal ground substance as is common to all concrement formation. They may be present in greatly variable amounts and in nearly all possible combinations. Pure cholesterol stones usually develop singly in the gallbladder. Since the work of Aschoff<sup>6</sup> and his collaborators, it has been generally accepted that they arise from stasis in the absence of infection, but in patients with altered cholesterol metabolism. Since they so frequently develop in connection with pregnancy, the finding of increased cholesterol in the bile, aspirated from the gallbladder during cesarean section, by Riegall, Ravdin and Morrison,<sup>7</sup> Boyden and Potter,<sup>8</sup> and at autopsy by MacNee,<sup>9</sup> lends support to the theory of stasis and altered cholesterol metabolism. Pure cholesterol stones, especially solitary stones, may be found in gallbladders showing no pathologic change, and cholecystography shows visualization by the dye in a high percentage of cases before complications have arisen (Graham<sup>10</sup>). The latter finding is evidence that cholesterol stones form in the presence of a relatively small amount of obstruction.

In contrast with these findings, pure calcium carbonate is known to be laid down in gallbladders, the seat of mild, chronic inflammation, with either complete or a very high grade obstruction of the cystic duct by calculi, as shown by the reports of Phemister, Rewbridge and Rudisill,<sup>11</sup> Phemister, Day and Hastings,<sup>12</sup> Cutler and Boggs<sup>13</sup> and others. It may occur as a separate deposit in the form of a stone, paste, or coarse sand, or as a layer on pre-existing stones. That the condition is not uncommon is shown by the fact that it was observed 23 times in 510 consecutive cases of operatively removed gallbladders in the University of Chicago Clinics. The recognition of the condition was due, in part, to the fact that roentgenograms were made of most

of the excised gallbladders, and then special attention was given to materials casting a calcium shadow during the pathologic examination

If bile has been completely excluded from the gallbladder for a long time, the calcium deposit will be white and the fluid scanty, clear and rich in mucus. If a small amount of bile enters, the contents will be somewhat pigmented, and the discolored calcium deposits may be easily overlooked. Inflammation of the gallbladder is either of low grade or absent during the period of calcium deposition. If the inflammation is more severe in the presence of cystic duct obstruction, hydrops or, rarely, empyema develops without calcium precipitation.

Appended are illustrative cases of pure calcium carbonate deposits in the presence of cystic duct obstruction by stone.

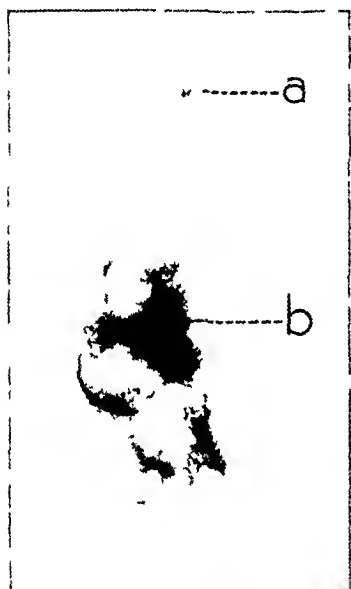


FIG 1—Case 1. Roentgenogram of gallbladder containing multiple cholesterol pigment stones with one stone in cystic duct (a) showing calcium carbonate shadow (b) in lumen.



FIG 2—Case 1. Gallbladder shown in Figure 1, opened. (a) Stone in cystic duct. (b) Calcium carbonate deposit.

**Case 1**—A B, male, age 54, has had occasional attacks of epigastric pain during the past five years, with one of increased severity in the last few days. Cholecystography revealed a calcium shadow lying high in the gallbladder region and nonvisualization of the gallbladder by the dye. At operation, the gallbladder was thickened, distended with fluid, and showed evidence of mild acute inflammation. It contained stones and there was a stone in the cystic duct. Some clear fluid was aspirated and the gallbladder removed, including the stone-bearing portion of the duct. A roentgenogram of the excised gallbladder (Fig 1) reveals the presence of faint shadows of multiple stones in the gallbladder and one stone in the cystic duct. In addition, there is a heavy shadow of material at the middle portion of the gallbladder and on the surface of some of the adjacent stones. On opening the gallbladder, a clear, viscid fluid escaped. It was found to contain numer-

ous brown, cholesterol-pigment stones, one of which was tightly wedged in the cystic duct. In addition, there was a white, soft deposit in the middle portion corresponding to the dense shadow shown in the roentgenogram. Some of it covered the surface of the adjacent stones (Fig 2). Chemical examination revealed its inorganic content to consist of calcium carbonate. Roentgenographic powder diagrams revealed lines of calcium carbonate in the form of small crystals of aragonite and larger crystals of calcite. Cultures of the fluid and wall yielded nonhemolytic *Streptococci*. The gallbladder wall was moderately thickened and, microscopically, showed slight round cell infiltration. This was a

FIG 3

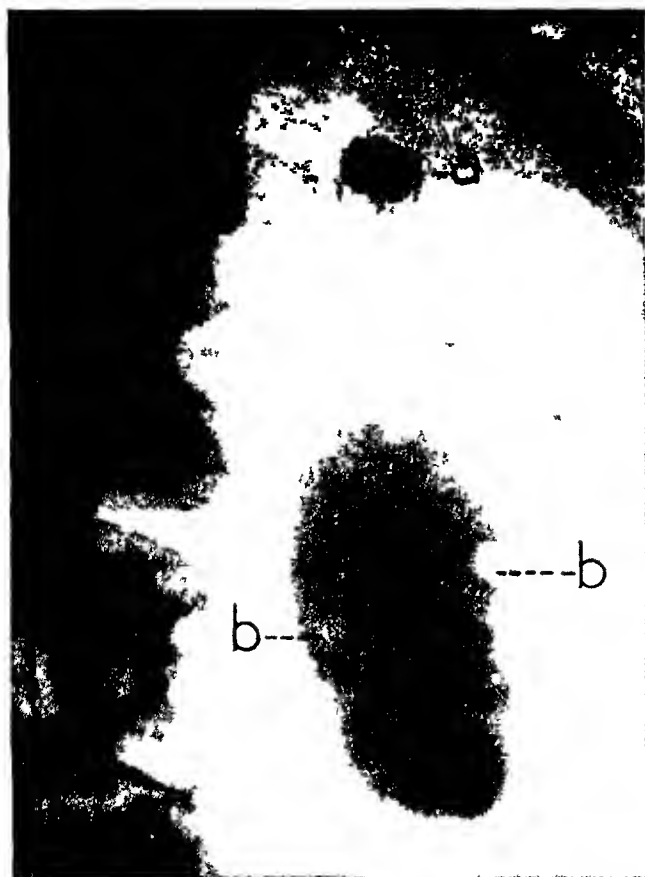


FIG 4



FIG 3—Case 2. Roentgenogram before dye administration. Radiopaque calcium carbonate on gallbladder side of stone in cystic duct (a); radiolucent shadow of cholesterol pigment stones (b) within calcium carbonate paste filling gallbladder.

FIG 4—Case 2. Roentgenogram of excised gallbladder. Cholesterol pigment stone in cystic duct with half moon shaped calcium shadow on the gallbladder side (a); cholesterol pigment stones (b) within calcium carbonate paste.

case of long-standing stones in the gallbladder, with calculous cystic duct obstruction and calcium carbonate deposition. There was superimposed a recent mild acute cholecystitis.

**Case 2**—T. M., female, age 59, had attacks of epigastric distress, with belching and occasional nausea and vomiting for four years, no jaundice. Cholecystography revealed a dense radiopaque shadow before dye administration filling most of the gallbladder region, with several radiolucent areas within. There was a dense radiopaque shadow above, in the region of the cystic duct (Fig 3). Roentgenogram following the administration of the dye showed no change in the shadows. At operation a stone was felt in the cystic duct. The gallbladder was about normal in size and there were adhesions constricting its proximal portion. The distal portion was filled with a soft mass. The adhesions were loosened and the gallbladder and stone-bearing portion of the duct re-

## COMPOSITION OF GALLSTONES

moved. A roentgenogram of the gallbladder (Fig 4) revealed a radiopaque substance scattered throughout the fundus and the narrow proximal portion of the gallbladder. There were small circular radiolucent shadows in the gallbladder most numerous in its narrow proximal portion. In the cystic duct there was the shadow of a stone, which was very radiopaque on the gallbladder side and radiolucent in its proximal two-thirds.

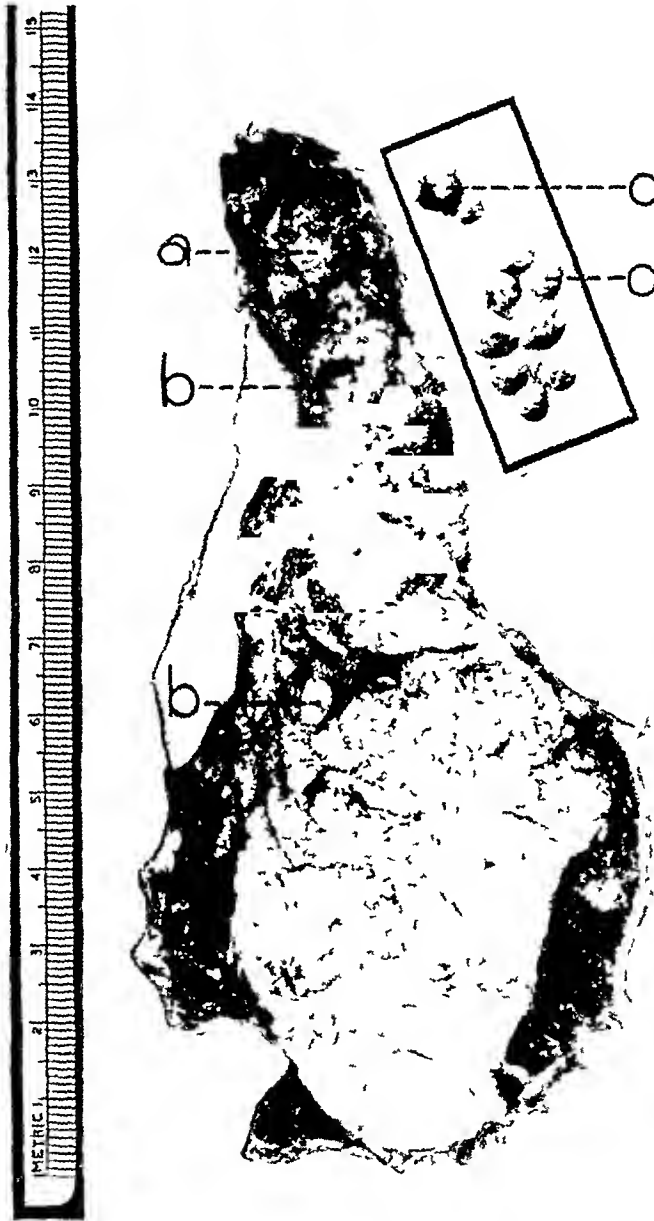


FIG 5—Case 2. Gallbladder and duct opened. Cystic duct stone (a), cholesterol pigment stones embedded in calcium carbonate mucus paste filling most of gallbladder (b). Inserted photograph of duct stone (c) and gallbladder stones (d).

The gallbladder and cystic duct were incised (Fig 5). The gallbladder was filled with a slightly greenish, putty-like, viscid material. There were several brown stones, measuring 3 to 5 Mm in diameter, scattered throughout it. The viscid material contained a grayish, thick, calcium deposit, and there was a thin white layer of calcium deposited on the surface of some of the stones. There was a cholesterol-pigment stone in the cystic duct, measuring roughly 1 cm in diameter, and on its gallbladder side there was a heavy grayish deposit of calcium which cast the opaque shadow in the roentgenogram (Fig 5,



a and b) The gallbladder, on microscopic examination, showed very slight cholecystitis. Cultures of the contents and wall remained sterile. Chemical examination of the putty-like mass revealed per 100 mg of dry material, 34.5 mg of calcium, 17.6 cc of CO<sub>2</sub>, and no phosphorus. This gives 86.25 per cent, if the calcium is calculated as calcium carbonate. Roentgenographic powder diagrams revealed lines of calcium carbonate in the forms of aragonite and calcite. The sequence of events was as follows. Cholesterol stones containing some pigment were laid down in the gallbladder. One of them had obstructed the cystic duct and a large pasty mass of calcium carbonate had then been precipitated in the gallbladder with only a very small amount of bile entering. There had been a heavy calcium deposit on the gallbladder side of the stone in the cystic duct and thin ring deposits of calcium on some of the other stones in the gallbladder.

Calcium carbonate precipitation in the gallbladder of animals, with the cystic duct ligated, has been reported by Wilkie<sup>14</sup> and by Phemister, Day and

FIG 6

FIG 7



FIG 6—Case 3. Roentgenogram before dye administration showing eight ring shadows of calcium density. Gallbladder did not visualize with dye.

FIG 7—Case 3. Roentgenogram of excised gallbladder. Radiolucent stone in cystic duct (a), calcium deposit in lumen (b) separate from that on the eight stones.

Hastings. A review of the clinical and experimental evidence leads to the conclusion that the calcium carbonate comes from the wall of the gallbladder, since the bile was completely excluded from the gallbladder in some of the cases and in the animal experiments. R. Schoenheimer (unpublished) analyzed one pure calcium carbonate stone, at this clinic, for copper and found 0.005 per cent, whereas other gallbladder stones contained 0.3 to 1 per cent, indicating that the bile which is the source of copper was excluded from the gallbladder while the calcium carbonate was being precipitated.

Aschoff has reported the finding of pure pigment stones in the gallbladder, but their occurrence is extremely rare, and no mention has been made of their

relation to obstruction Peel<sup>15</sup> analyzed such stones and found that they contained a high percentage of copper as compared with other gallstones

Falling between the pure cholesterol stone on the one hand, which forms with mild stasis, and little or no inflammation, and the pure calcium carbonate stone on the other, which forms with complete or very marked obstruction and mild chronic inflammation, are the great group of mixed stones. They develop usually in aggregations in a pathologic gallbladder, the cause of which is disputed, but which authorities, as Naunyn<sup>16</sup> and Aschoff, have considered as infectious, although cultures are sterile in a large percentage of cases. There is a fairly definite relationship between their contents of bile pigments, calcium and cholesterol and the degree of associated obstruction of the outlet. There may be fluctuations with time in the amount of pathologic change in the gallbladder and in the amount of obstruction produced either by the stone or by the inflammation, as a result of which the composition of the different layers of the stones may vary accordingly. In general, it may be stated that as stasis increases in gallbladders the seat of calculi, whether single or multiple, any deposit which may then be precipitated on the calculi shows a tendency to increase in calcium content, and also in bile pigments up to a point where the obstruction becomes very marked and the source of the pigment, the bile, is too greatly reduced. Such secondary deposits are dark in color from the increased pigment and usually cast radiopaque ring shadows in roentgenograms. That they may be laid down during periods of high grade obstruction of the cystic duct by a stone which itself may not receive a deposit is illustrated in the appended case



FIG 8—Case 3. Gallbladder opened. Soft cystic duct stone (a), separate calcium deposit in mucus (b). Gallbladder stones hard and dark green in color.

**Case 3**—M. H., female, age 44, had mild attacks of gallstone colic for several years, the last being one week before admission. Cholecystography revealed eight ring-shaped radiopaque shadows in the roentgenogram before dye administration (Fig 6), and non-visualization of the gallbladder by the dye. At operation, a stone was found in the cystic duct which could not be dislodged, and another one at the duct orifice which was easily moved back into the gallbladder. The gallbladder was removed along with the stone-

bearing portion of the cystic duct. It was little changed and slightly less distended than normally. A roentgenogram of the unopened specimen (Fig 7) showed eight ring-shaped radiopaque shadows in the gallbladder and one radiolucent shadow in the duct. There were also small separate shadows of calcium density about three stones at the fundus of the gallbladder. On opening the gallbladder, it was found to contain a small amount of greenish-stained mucous fluid and eight dark green stones. The cystic duct contained a soft yellowish stone (Fig 8). There was a small amount of grayish putty-like material about some of the stones at the fundus which cast the calcium shadow in the roentgenogram. Cultures of the bile and gallbladder wall remained sterile.

The stone in the cystic duct and one of the stones in the gallbladder were roentgeno-

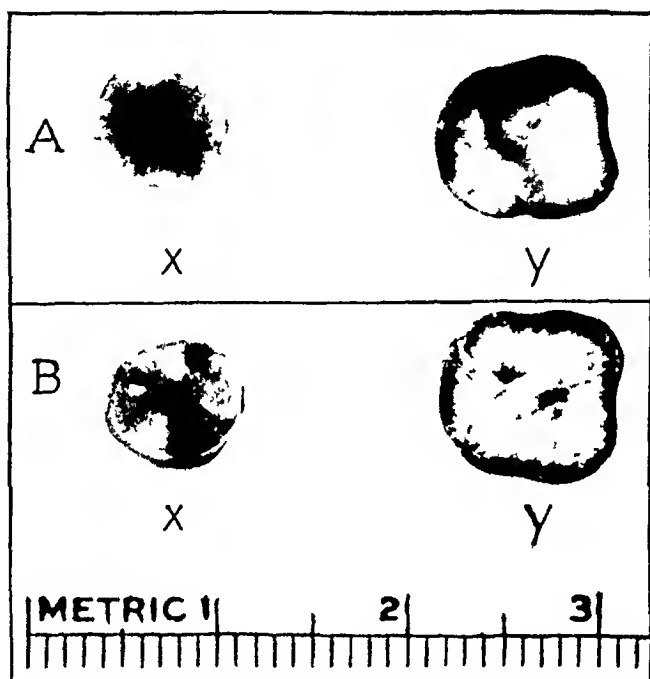


FIG 9—Case 3. A. Roentgenogram of the cystic duct stone (X) and one of the gallbladder stones (Y). B. Photograph of their cut surfaces showing a dark layer about the periphery of Y.

graphed and cut open, and their cut surfaces photographed (Fig 9). The cystic duct stone and the interior of the gallbladder stone were alike composed of cholesterol, the former being somewhat discolored by pigment. The gallbladder stone was covered by a dark green, hard coat casting a radiopaque shadow.

TABLE I

ANALYSES OF THE CALCULI IN CASE 3

	Cystic Duct Stone	Gallbladder Stone, Center	Gallbladder Stone, Periphery
	%	%	%
Ether extraction (weight)	81.2	86.2	38.7
Pure cholesterol (colorimeter)	35.7	40.3	15.4
Calcium	0.19	0.47	5.45
Phosphorus	—	—	0.05
Pigment	Trace	Trace	+
			Amount not determined

## COMPOSITION OF GALLSTONES

Chemical analyses (Table I) showed the coating on the gallbladder stone to consist of cholesterol, calcium and a small amount of pigment while its interior and the cystic duct stone were composed essentially of cholesterol. If the calcium is reckoned as present in the form of  $\text{CaCO}_3$  it amounted to 13.6 per cent. Roentgenographic powder diagrams of the stone from the cystic duct and of the central portion of a stone from the gallbladder showed lines of cholesterol and none of inorganic substances, while the shell of the latter showed lines of calcium carbonate in the forms of aragonite in a large amount and calcite in a small amount.

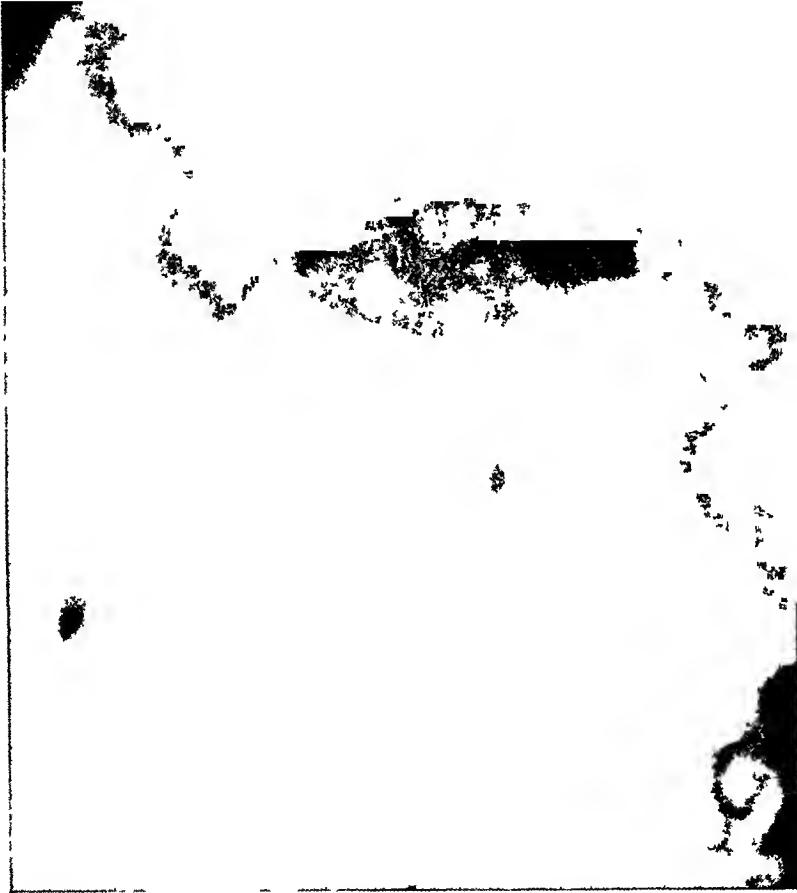


FIG. 10.—Case 4. Ring and cylinder shaped radiopaque shadows in gall bladder region. Gallbladder failed to visualize with dye.

The pathogenesis of the process was as follows. An aggregation of nine cholesterol stones formed in the gallbladder. One of them entered the cystic duct, producing marked obstruction, a layer consisting essentially of calcium carbonate, bile pigment and cholesterol was then deposited on the eight stones in the gallbladder, but the stone in the duct being more freely bathed in unobstructed bile did not receive a similar coating. At some stage in the process the obstruction had been very marked, and pure calcium carbonate in the form of a paste had been deposited in the fundus of the gallbladder.

Further proof of the importance of obstruction in the causation of second-

dary deposits rich in calcium and pigment on preexisting stones is the fact that if a gallbladder is largely filled and more or less partitioned by a row of stones, and if the outlet becomes incompletely blocked, calcium and pigment may be deposited on the stones in increasing amounts proceeding from the outlet to the fundus apparently as a result of increasing stagnation in the compartments created by the stones. No mention of this occurrence has been encountered in the literature, but it has been observed in varying degrees in five instances since it first came to notice one year ago, and is illustrated by the appended two cases

**Case 4**—N S, female, age 51, had attacks of epigastric and right upper quadrant pain, radiating to the back, at irregular intervals for several years, and entered the hospital four days after the onset of a mild acute attack. Cholecystography revealed in the roentgenogram taken previous to dye administration, ring and cylindrical shaped radiopaque shadows in the region of the gallbladder, and there was nonvisualization by the dye (Fig 10). At operation, a thick-walled, subacutely inflamed gallbladder, largely filled with stones, was found, and there was a stone in the beginning of the cystic duct. The gallbladder was removed and was found to contain, in addition to the calculi, a small amount of yellow mucinous fluid, cultures of which remained sterile, cultures of the wall showed diphtheroid bacilli. The stone in the first portion of the cystic duct was nodular and yellowish-gray in color. The three stones in the gallbladder were faceted and showed increasing pigmentation from ampulla to fundus (Fig 11). The stones were roentgenographed (Fig 12), sectioned with a fine jeweler's saw, and drawn in colors, to show the external and cut section appearances (Fig 13). The center of each composite stone in the gallbladder consisted of a cholesterol-pigment stone, similar to the one in the cystic duct. The four stones had formed in the gallbladder and one had entered the duct, after which the three in the gallbladder had grown from deposits which increased from cystic duct to fundus in pigment content, as shown by gross appearance and in calcium content, as shown by the roentgenogram. The roentgenogram revealed no calcium shadow on the stone in the cystic duct, an opaque cup-shaped calcium shadow on the distal half of the second stone, ring and band-shaped shadows on the third stone, and double ring-shaped shadows on the fourth stone, with a small radiopaque shadow at its center. A thin slice was cut from each stone. The slices were roentgenographed and samples taken from the different regions for chemical analyses, as indicated somewhat roughly in Figure 14. In general, they show the composition of the four central stones and of the secondary deposits, some samples consisting largely of the zones casting radiolucent shadows and others largely of pigmented material, casting radiopaque shadows. It was difficult to separate the materials sharply into radiopaque and radiolucent samples, the radiograms and roentgenographic powder diagrams afford, therefore, a better indication of the distribution of the calcium carbonate than do the chemical analyses. The four original central stones are rich in cholesterol and low in pigment and calcium with the exception of the nucleus of the fourth stone, in which there had apparently been a secondary deposit of calcium. This had probably taken place in a cavity created by swelling and shrinkage, as is not uncommonly found in gallstones. While the results of the analyses are somewhat inconstant, the secondary peripheral deposits laid down during duct obstruction showed proportionately much more pigment and calcium, and less cholesterol than the central portions.

Roentgenographic powder diagrams were made at the periphery of the stone in the fundus of the gallbladder. They showed lines of a finely divided material having a structure resembling that of dahlite and apatite, which are complex compounds of tricalcium phosphate and calcium carbonate.

**Case 5**—D M, female, age 51, gave a history of occasional mild attacks of gallstone colic over a period of ten years, and was admitted to the hospital two days after

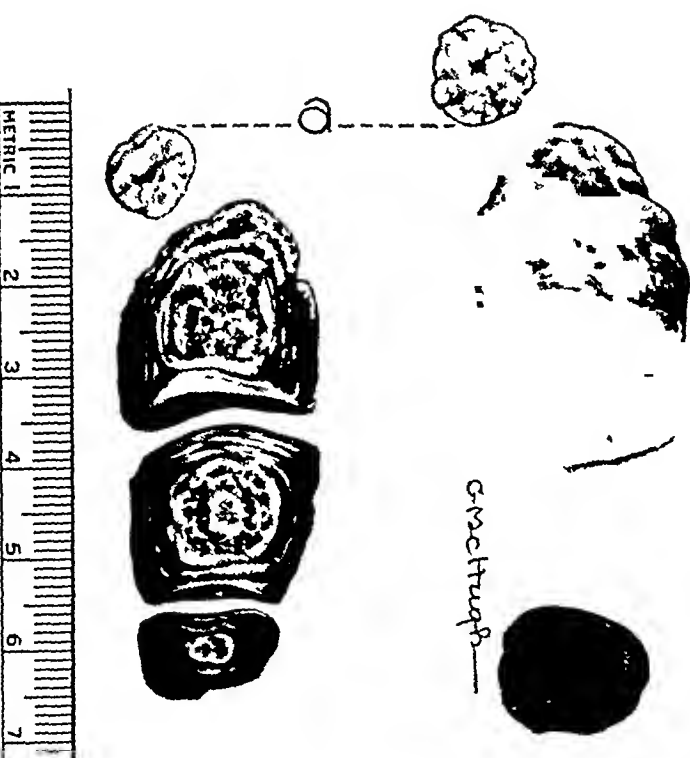
Fig 11



Fig 12



Fig 13



- Fig 11—Case 4 Gallbladder opened (a) Stone in cystic duct  
 Fig 12—Case 4 Roentgenogram of stones Cystic duct stone (a) casts no calcium shadow  
 Fig 13—Case 4 External and cut surface appearance of stones Cystic duct stone (a) of same appearance as central portion of the three composite stones in the gallbladder



COMPOSITION OF GALLSTONES

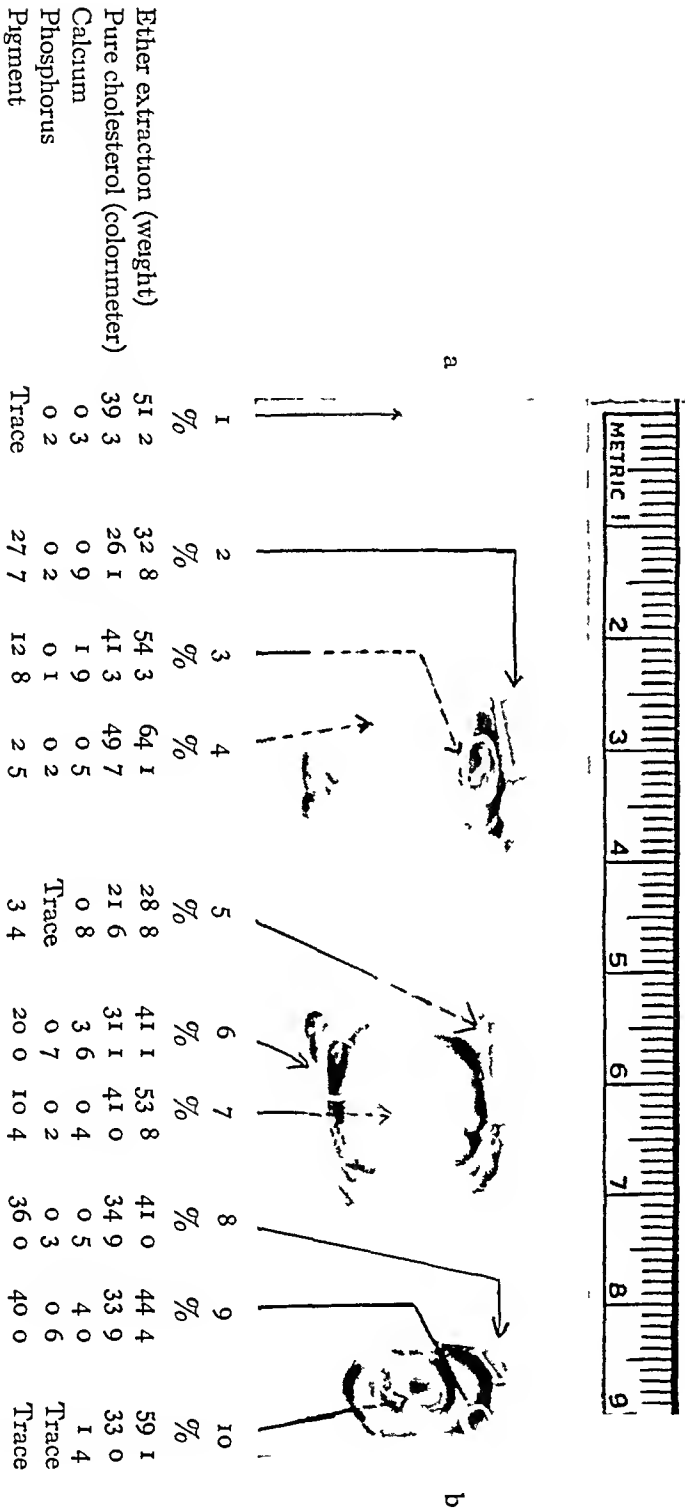


Fig. 14.—Case 4. Roentgenogram of slices of stones, arranged from cystic duct (a) to fundus (b), showing, roughly, regions analyzed chemically, and an appended tabulation of the analyses.



the onset of an attack. Cholecystography revealed a row of radiopaque shadows in the roentgenogram before dye administration, the one in the fundus region being the most dense. There was no visualization of the gallbladder by the dye (Fig 15). Six weeks later, after subsidence of the acute cholecystitis, the gallbladder was removed. It was long, thick-walled, and filled with four large stones. A roentgenogram (Fig 16) shows radiopaque calcium shadows in the second, third and fourth stones, increasing in intensity away from the radiolucent stone at the ampulla. On opening the gallbladder, one stone was found engaged in the ampulla. There were about 10 cc of serosanguineous fluid that contained numerous black particles about 1 Mm in diameter. Cultures yielded a microaerophilic *Streptococcus*. The stone in the ampulla was yellowish-red in color. The other three stones were faceted and externally were increasingly dark in color from am-



FIG 15—Case 5. Gallstones in gallbladder casting radiopaque shadows of increasing density toward fundus (a). Nonvisualization of gallbladder by the dye.

pulla to fundus. They were sectioned longitudinally with a jeweler's saw, and color drawings to scale were made to show the distribution of the pigment (Fig 17). The centers of all four stones consist of a yellowish (cholesterol) zone, measuring  $1\frac{1}{2}$  to 2 cm in diameter. Apparently, the four original stones had formed simultaneously, and the proximal stone then obstructed the ampulla, after which there were lamellated secondary deposits on all of them. The deposit on the proximal stone appears grossly to be of essentially the same material as the original, that on the second stone showed slightly more brownish pigmentation, and that on the third stone showed yellowish-brown pigmentation of the proximal, and deep brown to black pigmentation of its distal portion. That on the fourth stone showed brown to black pigmentation. Slices were cut from the four stones, roentgenographed, and samples taken roughly of the various portions for chemical analyses (Fig 18). The central stones were rich in cholesterol and low in calcium and pigment. The periphery of the stones showed calcium increasing in amount from the ampulla to

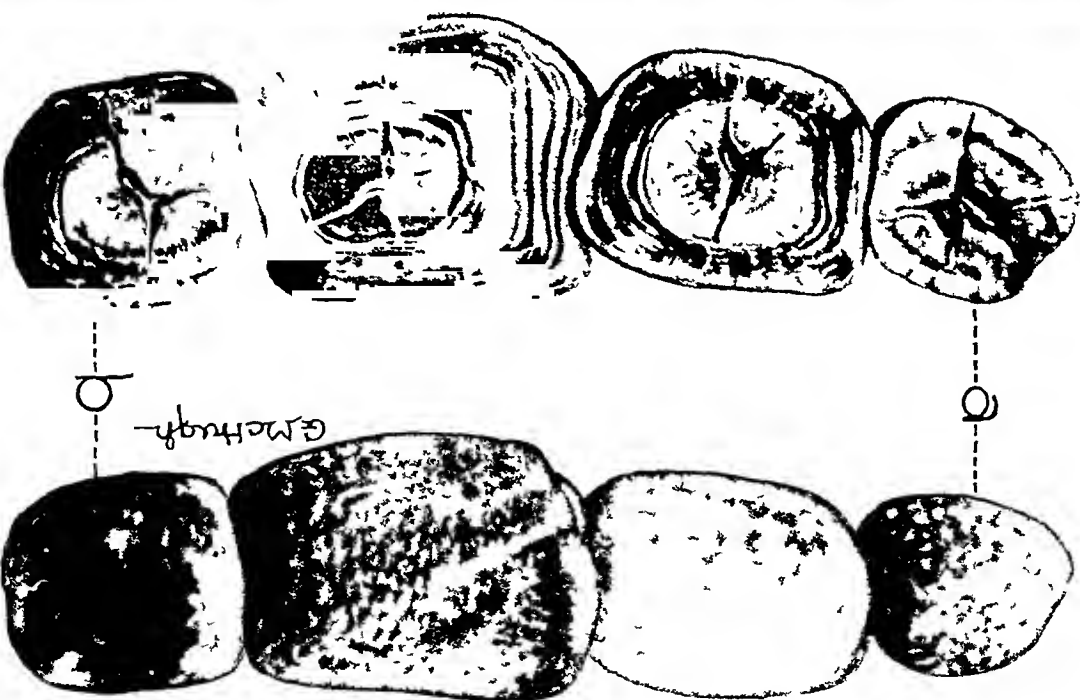


Fig 17

Fig 16—Case 5 Roentgenogram of exised gallbladder shows calcium shadows in increasing depths in stones from the ampulla (a) to fundus (b)  
 Fig 17—Case 5 Lateral and cut sections of stones, centers of all four stones similar Surface deposits show increased pigmentation from ampulla (a) to fundus (b)



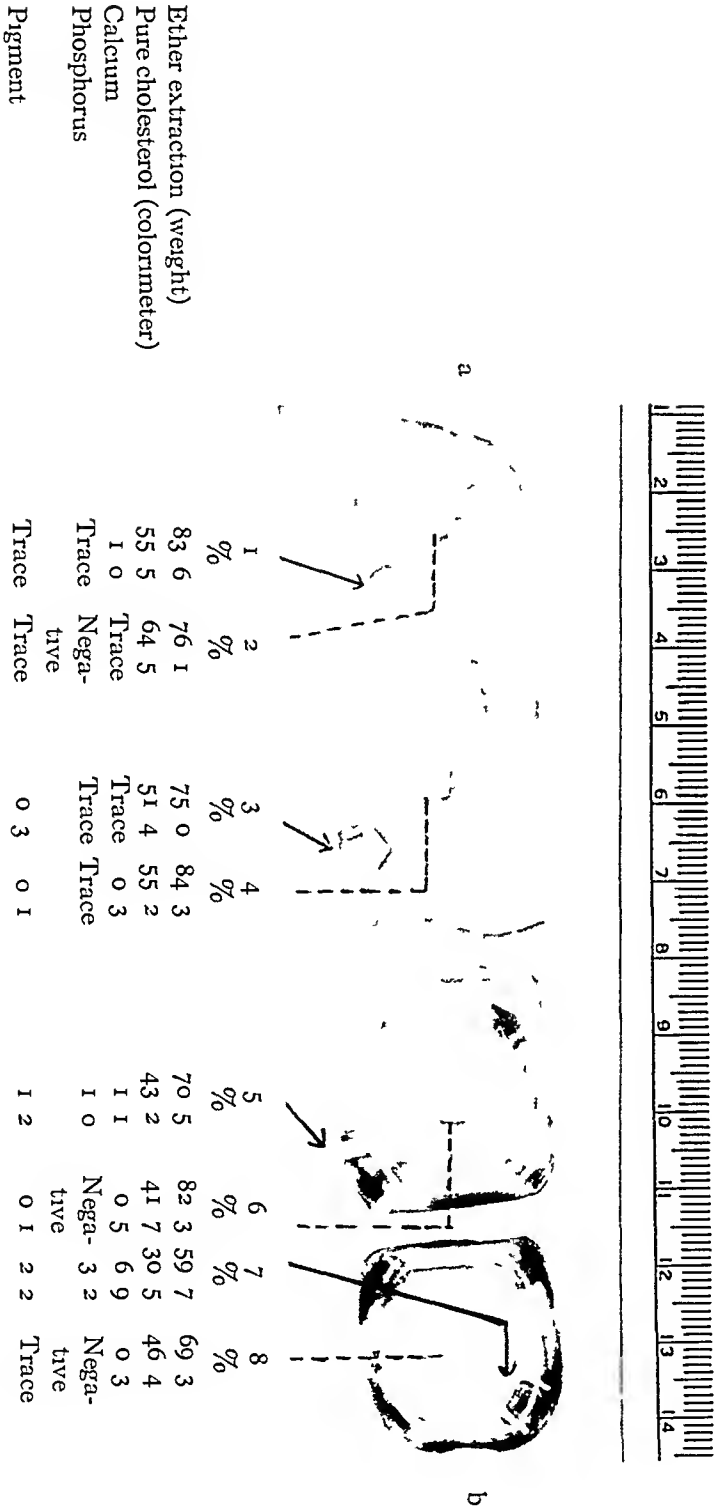


FIG. 18.—Case 5. Roentgenogram of slices of stones arranged from ampulla (a) to fundus (b) showing regions analyzed chemically, and an appended tabulation of the analyses.

fundus While the pigment of the periphery of the stones also increased in amount from the ampulla to the fundus, the figures show a much smaller amount than would be expected from the gross appearance (Table III) This suggests that some of the pigments were not detected by the method of analysis employed or other coloring matter was present

Roentgenographic powder diagrams were made of the periphery of the stone in the fundus of the gallbladder They revealed lines identical with those found in the stones in Case 2

When one end of a gallstone is engaged in the ampulla of the gallbladder, it is not uncommon for calcium and pigment to be deposited on the other



FIG 19—Case 6 Gallstone shadow, gallbladder did not visualize with dye

end as a result of the stagnation which it produces This has been seen in four cases and is illustrated by stone 1 in Figure 24

Surface deposits rich in calcium and pigment are often found on both single and multiple stones without any accompanying stone obstruction of the cystic duct or ampulla being found at operation or autopsy The question arises whether they were laid down during a period of inflammatory obstruction or temporary stone obstruction That obstruction may be a factor, is supported by the finding that in the great majority of cases of cholelithiasis with stones casting a radiopaque (calcium) shadow there is non-visualization of the gallbladder by the dye, as reported by Graham<sup>10</sup> and Phemister, Day and Hastings<sup>12</sup> The condition is illustrated by the following case

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Case 6—M P, female, age 66, had had indefinite attacks of epigastric distress at intervals for four months. A roentgenogram (Fig 19) revealed a large radiopaque shadow in the gallbladder region, with an oval center which was less dense than the thick periphery. There was no change in the shadow after dye administration. At operation, no stone was found in the cystic duct. The gallbladder was removed. It was moderately thickened and contained a small amount of dark, stringy bile and a dark



FIG 20—Case 6 (a) Photograph of exterior and (b) of cut surface of stone (c) Roentgenogram of slice. Central portion is a cholesterol stone. Dark periphery consists of pigment, calcium carbonate, and cholesterol.

TABLE IV  
ANALYSIS OF THE CALCULUS IN CASE 6

	Periphery %	Center %
Ether extraction (weight)	18.5	55.5
Pure cholesterol (colorimeter)	8.7	44.2
Calcium	4.96	0.25
Phosphorus	2.0	0
Pigment	5.8	Trace

brown oval stone, measuring 5.2x3 cm (Fig 20a). Section of the stone showed it to consist of a grayish, crystalline, cholesterol center and a thick greenish-brown, lamellated periphery (Fig 20b). A roentgenogram of a somewhat fragmented slice (Fig 20c) reveals a radiolucent center and a lamellated radiopaque periphery, showing that the calcium density is confined to the pigmented portion.

Chemical analysis (Table IV) showed the central portion rich in cholesterol. The peripheral portion revealed proportionately less cholesterol, but substantial amounts of calcium, pigment and phosphorus. Roentgenographic powder diagrams of the peripheral portion showed lines of calcium carbonate, chiefly as calcite but also as aragonite and vaterite B.

Little attention has been given to the condition of the cystic duct in such cases, but it is possible that a careful examination at operation or autopsy would reveal evidence of some degree of inflammatory obstruction. The possibility of functional obstruction or dyskinesia of both the cystic duct and the ampulla of Vater has been advocated by Westphal,<sup>17</sup> and of kinking adhesions and anomalous folds of the cystic duct by Cole.<sup>18</sup> Secondary changes in gallbladder, including infection, complicating one of these conditions might lead to calculus formation with the deposition of layers rich in pigment and calcium.

While single or multiple mixed stones may remain uniform in composition, fluctuations in cholesterol, pigment and calcium content may occur from their incipency, giving rise to many layers which vary both in chemical

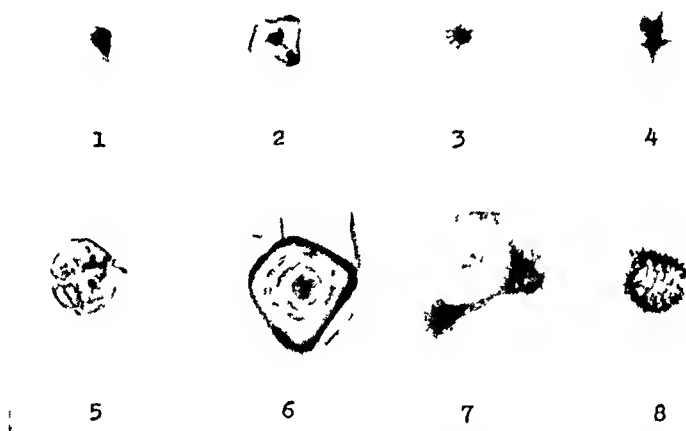


FIG. 21.—Roentgenogram of stones removed from different gall bladders showing different arrangements of radiopaque calcium carbonate shadows.

composition and in thickness, thus a nucleus may be rich in calcium and pigment, or there may be one or more layers, rich in calcium and pigment, deposited at intervals as the stone grows, which alternate with layers made up of cholesterol and pigment only. Rarely, there is a radiating arrangement of the materials rich in calcium and pigment. Figure 21 shows roentgenograms of stones removed from the gallbladders of different patients, in whom no stone obstruction of the cystic duct was found. Their dense areas indicate that they contained calcium, variously distributed in nucleus, internal and external layers, and even in rays and in clefts. There is little concrete evidence at hand as to the presence or absence of obstruction at the time the calcium was deposited. In the cases analyzed, the calcium was present along with pigment and cholesterol in somewhat the same proportions as found in the layers of stones in the preceding cases in which there was stone obstruction of the duct. The similarity suggests that these deposits were laid down during periods of temporary obstruction by inflammation or, less likely,

by spasm or by stones which subsequently passed the cystic duct. The star-shaped deposits of calcium in clefts of multiple stones (Fig 21, 4) that have formed, according to Bauer,<sup>19</sup> as a result of swelling followed by shrinkage and transformation from spherical to polyhedral forms, may be further evidence of the rôle of stagnation in calcium deposition, since the fluid permeating the clefts becomes stagnant. That very high grade inflammatory obstruction of the cystic duct may occur is demonstrated by the occasional finding of a mucocele of the gallbladder in which bile has been completely excluded by duct swelling for a long period of time as in the following case.

**Case 7**—W. E., male, age 36, had had vague distress in the epigastrium and right upper quadrant, coming on usually at night, lasting for two or three hours. There was residual soreness for 12 to 24 hours, and the attacks gradually increased in frequency over a period of eight months. Cholecystography revealed no radiopaque shadow in the



FIG 22—Case 7. Mucocele of the gallbladder resulting from inflammatory obstruction of cystic duct (x).

gallbladder region, and there was nonvisualization of the gallbladder by the dye. At operation, a moderately thickened gallbladder, somewhat smaller and much more tense than normal, was found. There were no stones palpable, either in the gallbladder, or cystic or common duct. The gallbladder was removed. On section, it was filled with clear, very thick mucus which was irregularly dotted with white and a few black, soft, flocculent areas. No stones were found (Fig 22). Smears of the black areas showed them to consist very largely of pigment and a few cholesterol crystals. On the other hand, the light specks consisted very largely of cholesterol, with a small amount of pigment. The short portion of the cystic duct, which was excised, was swollen, but when cut open a lumen was present. Cultures of the gallbladder and mucus were sterile. Microscopic sections of the gallbladder showed slight edema and round cell infiltration of the wall.

Obstruction in this case was of such high grade that calcium carbonate might well have been thrown out as a free deposit in the gallbladder, since the mucus which it contained was freer from biliary content than was found in some of the observed cases of pure calcium carbonate deposition in the gallbladder.



*Stone Formation in the Bile Ducts*—In contrast to the marked variation in composition of stones formed in the gallbladder are the relative uniformity of composition of stones formed in the bile ducts and the paucity, or absence, of calcium carbonate.

Stone formation there is usually preceded by stone formation in the gallbladder, and it is set up after calculi have passed into the common duct with resultant cholangic obstruction and infection. Rarely, it may occur independent of cholecystolithiasis, as in cirrhosis of the liver (McIndoe and Judd<sup>20</sup>), or in carcinomatous obstruction of the ducts (Lampert and McFetridge<sup>21</sup> and Marshall<sup>22</sup>), and the stones may even form in the intrahepatic radicals. When the stones have been laid down in the presence of calculi which came from the gallbladder, the question arises as to whether or not it is possible to distinguish between the two. However, stones formed in the ducts after removal of the gallbladder and of stones from the common duct, afford opportunity to obtain accurate information about the composition of the material laid down there. The following three cases of this type have been studied.

Case 8—B. R., female, age 59, married, had had an attack of gallstone colic with jaundice, in 1932. She was operated upon by Dr. A. F. Henning, who removed the gallbladder, which contained several light to brown stones, and three brown stones were removed from the common duct. The patient remained well for two years, after which she had occasional attacks of pain in the epigastrium, nausea and vomiting lasting for short periods and sometimes followed by jaundice. For three months before admission to the University of Chicago Clinics, December 13, 1936, she had had attacks of pain accompanied by chills and fever and followed by jaundice. The examination on admission showed her in fairly good general condition, afebrile, and free from jaundice and bile in the urine. There was moderate tenderness in the right hypochondrium. At operation, December 16, 1936, stones were felt in the common duct, which was inflamed and markedly enlarged. On opening the choledochus, a large stone was found just above the ampulla of Vater. It was removed along with about 150 smaller stones which were in the dilated common and hepatic ducts above. A catheter was then inserted and many small stones, of similar appearance, were washed from the intrahepatic radicals. Cultures of the bile showed *B. coli*, Streptococci and *B. proteus*. T-tube drainage was established and maintained for three and one-half weeks. The ducts were irrigated daily and several small stones were subsequently washed from them. The patient has since remained free from symptoms. Figure 23 is a photograph of the stones removed from the ducts. Attempts to pass a probe through the ampulla of Vater were unsuccessful.

Section of the large stone and of several small stones showed them to consist of a uniformly dark, greenish-brown, soft material. There was no separate center in the large stone to suggest that it represented a gallbladder stone that had been left in the common duct at the previous operation.

Chemical analysis revealed cholesterol (impurities included) 65.8 per cent by weight, and 55.9 per cent by colorimetric determination, bile pigments 12.7 per cent, calcium, a trace (not measurable), phosphorus negative. Roentgenographic powder diagrams revealed no lines of calcium carbonate or other inorganic substance.

Since all the stones were of uniform structure and composition, and since the stones washed from the intrahepatic ducts must have been formed there, it is safe to say that these were calculi which were formed within the ducts.

Failure to pass a probe into the duodenum may have been due to temporary swelling but it may have indicated some degree of permanent narrowing of the ampulla which, as well as the infection, was a factor in causing the stone formation

**Case 9**—C R, male, age 53, was first admitted May 3, 1930, with the following history In 1912, he had had recurrent attacks of right upper quadrant pain and a cholecystostomy was performed, at which time a large cholesterol stone was removed which the patient saved (Fig 24, 1) There were recurrent attacks after three years which, in 1918, were associated with jaundice A cholecystectomy was then performed, and the pathologist's report was that the gallbladder contained several stones About three years later he began to have mild attacks of right upper quadrant pain which recurred irregularly until 1928, when they became more severe and were accompanied by chills, fever and jaundice He entered the hospital in 1930 because of recent attacks

Physical examination was essentially negative aside from tenderness in the right

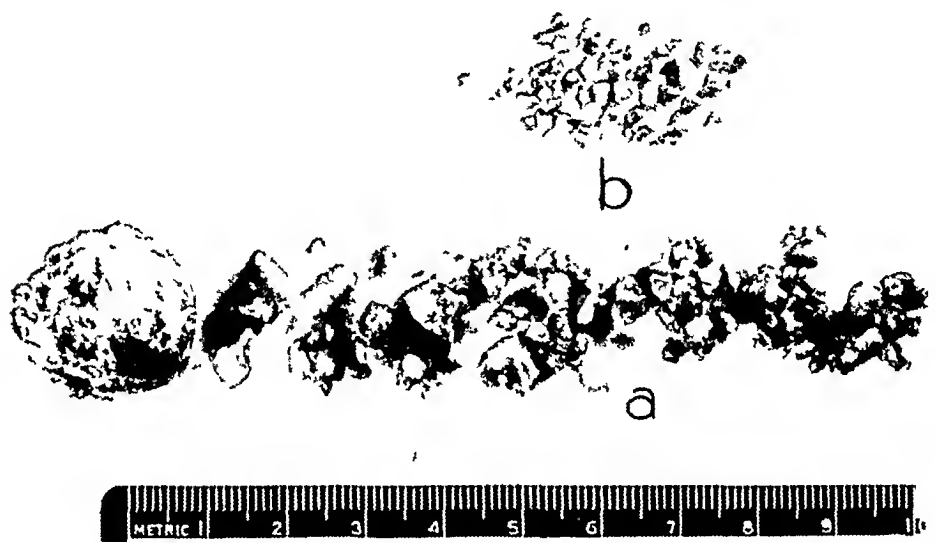


FIG 23—Case 8 Stones removed from common and hepatic ducts (a) and intrahepatic ducts (b), which formed after cholecystectomy and choledocholithotomy

upper quadrant Cholecystography revealed no shadow of either gallbladder or calcified stone At operation a dark stone, about 2 cm in diameter, was removed from the common duct (Fig 24, 3) He remained well for over a year and then had attacks of right upper quadrant pain In March, 1935, an attack was followed by jaundice which continued in mild form until readmission three months later Physical examination was then essentially negative except for slight jaundice A roentgenogram of the biliary region was negative for radiopaque stone shadows At operation, June 21, 1935, seven large reddish-brown stones were removed from the dilated and infected common and hepatic ducts (Fig 24, 4) The ampulla of Vater was patent Cultures yielded *B coli*, Streptococci and *Cl welchii* There was T-tube drainage for one month Beginning three and one-half months after operation, the patient had an attack of right upper quadrant pain and slight jaundice Similar attacks recurred and he was again operated upon, February 28, 1936, at which time a soft reddish-brown stone, 1½ cm in diameter, was removed (Fig 24, 5) A catheter was introduced into the hepatic radicals and numerous very small dark stones resembling sand were washed out The ampulla of Vater was patent Cultures of the fluid yielded *B coli*, hemolytic Diplococci and *Cl welchii* T-tube drainage was maintained for five months subsequently with daily irrigations Small dark pigmented stones were occasionally washed from the duct over a

period of weeks The patient has remained well for two years following the removal of the T-tube

A roentgenogram was made of the stones removed at the first, third, fourth and fifth operations (Fig 24) The only shadow of calcium density is that on the surface of

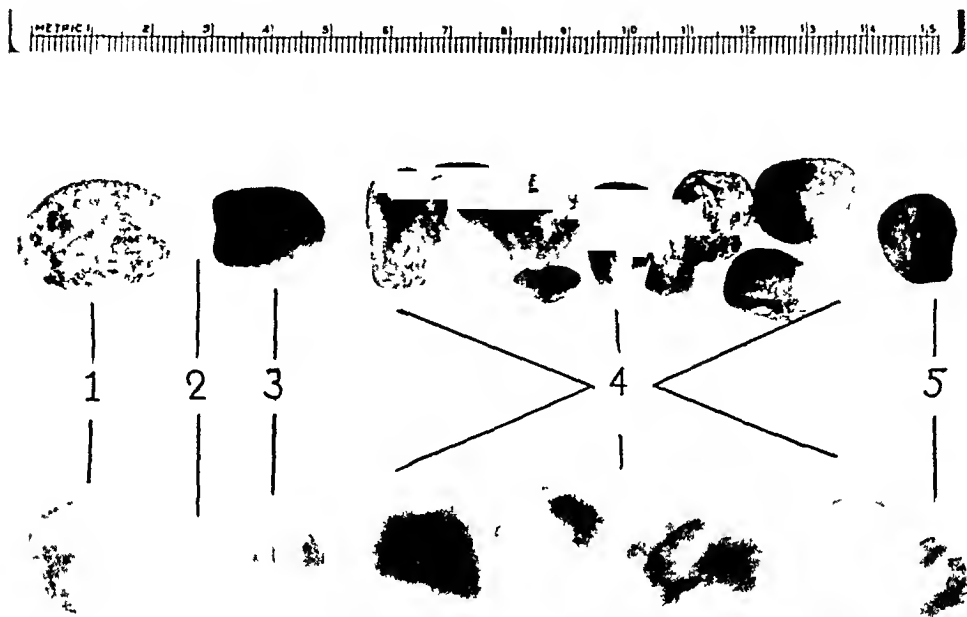


FIG 24—Case 9 Photograph above and roentgenogram below Stone removed from gallbladder (1) Cholecystectomy in interval (2) Stone removed from common duct at third operation (3), fourth operation (4) and fifth operation (5)

TABLE V

ANALYSES OF THE CALCULI REMOVED AT THE VARIOUS OPERATIONS UPON CASE 9

Stone	First Oper No 1912	Third Oper No 3152 Periphery	Third Oper No 3152 Center	Fourth Oper No 8934	Fifth Oper No 9771 Mixture	Bile Duet Washings
Ether extraction (weight)	76 0%	60 5%	78 7%	55 0%	34 5%	36 0%
Pure cholesterol (colorimeter)	49 7%	31 7%	42 4%	49 5%	19 9%	Not Deter mined
Calcium	Rt end neg Lft end 3 0%	Negative	Negative	1 05%	1 1%	1 8%
Phosphorus	Negative	Negative	Negative	Negative	Negative	Negative
Pigment	0 3%	9 1%	2 1%	21 2%	14 8%	42 0%

one end of the stone removed from the gallbladder which probably had been deposited while the other end was obstructing the ampulla Sections were made with a jeweler's saw of the stones removed at the first and third operations and of one stone from the fourth operation (Fig 25) The one removed at the first operation is a solitary chole-

## COMPOSITION OF GALLSTONES

terol stone with a thin, hard crust on one end. The stone from the common duct at the third operation consists of a thick, reddish-brown outer layer deposited on a light yellow central stone. That from the common duct at the fourth operation is reddish-brown except for a dark black debris at the center, which possibly represents an old blood clot. Since the outer layer of the second stone resembles the third stone and also the one removed at the fifth operation, it is highly probable that it was deposited in the duct on the lighter central stone which had migrated there from the gallbladder. This view is supported by the fact that the patient had been jaundiced before the second operation at which the gallbladder containing multiple stones was removed. The very small pigmented stones washed from the intrahepatic ducts at the last operation were the same in color and consistency as the larger stones. The chemical analysis of the stones is given in Table V.

Roentgenographic powder diagrams showed lines of calcium carbonate in the form of vaterite and calcite in the surface coating on the left end of stone 1, and none in the stones that were formed in the common and hepatic bile ducts. They showed cholesterol lines in all the stones.



FIG 25—Case 9 Sections of stones from first, third and fourth operations

In brief, the stones known to be formed in the common, hepatic and intrahepatic ducts were rich in cholesterol and bile pigments and very low in calcium. The center of the first stone removed from the common duct appeared to have come from the gallbladder and to have been the obstructing factor which helped to set up stone formation in the ducts. Prolonged drainage and irrigation of the ducts after the last operation appeared to help clear up the infection and get rid of the stone forming tendency.

**Case 10**—R. F., male, age 66, entered the hospital in October, 1932, with a history of attacks of gallstone colic extending over a period of three years, most of which had been accompanied by fever and jaundice. He was then in a free interval but the urine contained a trace of bile. At operation, October 14, 1932, a thickened and adherent gallbladder, free from stones, was removed. The dilated and thickened common duct was opened and eight stones removed from it (Fig 26, a). There appeared to be pocketing of the duct near the ampulla of Vater and one stone was removed from it with great difficulty. A probe was passed into the duodenum. The common duct drainage was con-

tinued for 21 days. About one year later the patient had recurrence of the right upper quadrant pain accompanied by slight chills, fever and jaundice. These continued at irregular intervals for about two and one-fourth years, at which time the trouble grew worse and the jaundice became persistent. He was readmitted to the hospital, April 23, 1935, with mild jaundice and bile in the urine. At operation, May 6, 1935, one large and about ten soft, small, dark reddish-brown stones were removed from the common duct (Fig 26, b). The large stone was engaged in a pocket just above the ampulla of Vater and was extracted with difficulty. Cultures of the bile yielded a heavy growth of *B. coli*, *Staphylococci* and *Streptococci*. The duct was closed with catheter drainage, leakage of bile and duodenal contents, however, developed subsequently, resulting in death from peritonitis, eight days after operation. Autopsy revealed suppurative peritonitis, a large pocket of the first portion of the common duct and a few soft brown stones in ducts within the liver.

Sections were made of the stones removed at the first operation. They consisted of a white crystalline interior coated by a dark reddish-brown layer, measuring 1 to 2

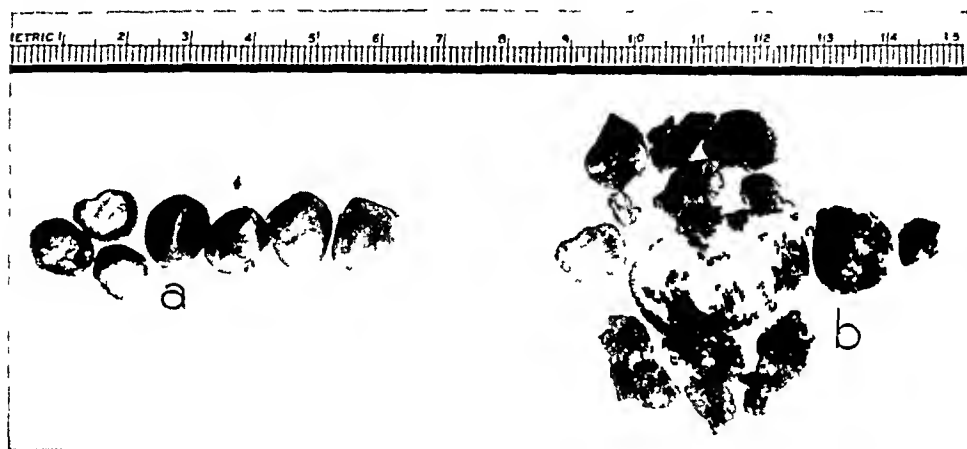


FIG 26—Case 10. Stones removed from common duct at first operation (a), and at second operation (b).

Mm in thickness. Section of the large oval stone, 3 cm long, removed at the second operation, revealed a central white portion similar to the centers of the stones removed at the first operation. This was covered by a reddish-brown intermediary layer of the same thickness and nature as the coating of the stones at the second operation and by a thick brown layer outside this, which evidently represented a deposit on a stone left in the pocket at the first operation. The other stones from the second operation were composed of this same brown material. Figure 27 shows a cross section of one of the small stones removed at the first operation and of the large stone removed at the second operation after much of its soft surface portion had crumbled off.

Chemical analyses were made of the light central and reddish-brown peripheral portions of the stones, shown in Figure 27, removed at the two operations, and of the soft brown stones removed from the intrahepatic ducts at autopsy (Table VI).

Roentgenographic powder diagrams were made of the portions of stones that were analyzed chemically. They showed lines of cholesterol but no lines indicative of calcium carbonate or other inorganic contents.

The order of development in this case appears to have been as follows. An aggregation of cholesterol stones formed in the gallbladder, which migrated to, and obstructed, the common duct. Then stone formation was set up in the ducts and a reddish-brown coat of pigment and cholesterol was deposited

# COMPOSITION OF GALLSTONES

on each stone Cholangitis was present Following operation, at which one stone was left in the common duct, there was continued infection and stagnation in the duct pocket This led to further stone formation in the intra- and extrahepatic ducts of the same general character as the deposit previously laid down on the stones from the gallbladder

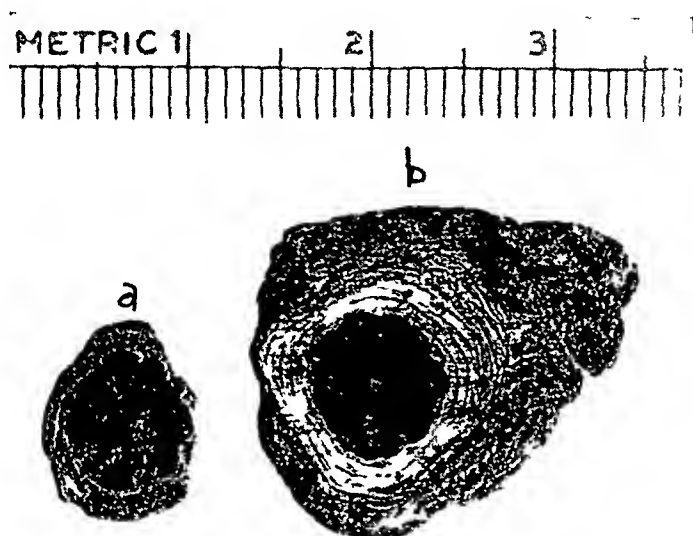


FIG 27—Case 10 Sections of stone from first operation (a) showing cholesterol center and periphery of cholesterol pigment, and from second operation (b) showing center stone of same nature as (a) with deposit on outside

TABLE VI

ANALYSES OF THE CALCULI REMOVED AT THE TWO OPERATIONS UPON CASE 10

Stone	(a) Center %	(a) Periphery %	(b) Center %	(b) Intermediary %	(b) Periphery %
Ether extraction (weight)	91.5	31.8	90.0	34.8	56.8
Pure cholesterol (colorimeter)	46.9	16.8	54.1	19.7	21.8
Calcium	0.52	0.95	0.64	0.49	1.08
Phosphorus	—	—	—	—	—
Pigment	Trace	25.5	Trace	25.3	22.1

*Discussion*—In all three cases, obstruction of the common duct by a stone or stones migrating there from the gallbladder appears to have preceded the setting up of stone formation in the ducts Infection was present in all cases and obstruction and infection appeared to have been causative factors in the reformation of stones after gallbladder and common duct stones had been removed However, additional causative factors that were active in the gallbladder were possibly also active in the ducts There was little variation in the composition of the stones, which consisted in the three cases of pigment and cholesterol with very little or no calcium

Reformation of stones after cholecystectomy and choledocolithotomy, should

be more frequent if the stone forming tendency has already been set up in the ducts, and if some degree of infection and obstruction persist postoperatively. Benign stricture of the common or hepatic ducts, resulting from injuries at operation, are usually not accompanied by stone formation within the ducts. In nine cases operated upon in this clinic, there was the presence of a small amount of brownish mud in two cases, which resembled, grossly, small amounts of material present in the three cases of recurrent stones in the ducts. The failure of development of stones in such cases may be related to the fact that injury is usually of a duct not containing stones and consequently neither infected nor obstructed nor possessing the stone forming tendency.

**SUMMARY**—Stones found in the gallbladder vary greatly in their contents of cholesterol, pigment and inorganic calcium salts, one important cause of which is variation in the amount of associated obstruction of the cystic duct. Stones very rich in cholesterol may form in the gallbladder when stasis is mild, as judged by the great frequency of dye visualization, and when inflammation is mild or absent, as judged by pathologic examination. With increasing chronic obstruction of the cystic duct there is a tendency for increasing amounts of calcium and bile pigments to be laid down on the preexisting stones in the gallbladder.

If large stones partition the gallbladder, causing increasing stagnation within, from ampulla to fundus, there is a tendency for any further growth of the stones to consist of materials which increase in pigment and calcium contents from ampulla to fundus. With complete, or almost complete, obstruction of the cystic duct in the presence of low grade chronic cholecystitis, calcium carbonate alone may be precipitated from the gallbladder fluid as a whitish deposit either about the preexisting stones or as a separate mass.

In contrast with these findings, stones formed in the bile ducts vary relatively little in building materials consisting of bile pigments and cholesterol with very little or no calcium. Obstruction is an important cause of stone formation in the ducts, since it is usually set up in the presence of a stone from the gallbladder which has lodged there. Persistent cholangitis, with some degree of inflammatory obstruction, appear to be factors in the reformation of stones in the ducts after cholecystectomy and choledocholithotomy.

Calcium is present very largely as calcium carbonate, which may be in the specific crystalline forms of aragonite, calcite or vaterite B, as shown by roentgenographic powder diagrams. However, calcium was present in two cases of gallbladder stones, partitioning and obstructing the gallbladder in a form resembling dahlite.

The source of the calcium carbonate is the wall of the gallbladder, in case it is thrown down within the gallbladder while the cystic duct is completely obstructed by a stone.

Its source is also the wall of the gallbladder, when it is deposited in

layers on gallbladder stones in the presence of high grade but incomplete stone obstruction of the cystic duct as in Case 3. The findings that calcium is laid down in the gallbladder, when its outlet is obstructed, and that stones formed in the ducts contain little or no calcium, are highly indicative that the calcium salts of gallstones are derived from the wall of the gallbladder, and that little or none come from the bile.

The source of the cholesterol of calculi formed in the common duct after removal of the gallbladder is doubtless the bile.

The view that the cholesterol of gallstones formed in the gallbladder is also derived from the bile is favored by the finding of a decreased cholesterol content of gallstones formed with increased obstruction of the common duct, while their calcium and pigment contents are increased, also by the absence of cholesterol deposition when calcium carbonate is deposited within the gallbladder in the presence of complete obstruction of the cystic duct.

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# FURTHER EVIDENCE THAT PANCREATIC JUICE REFLUX MAY BE ETIOLOGIC FACTOR IN GALLBLADDER DISEASE\*

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It is obvious to anyone who has had much experience with biliary tract surgery that there are factors concerning biliary tract pathology which are not understood at the present time. As recently as January, 1938, Clute,<sup>2</sup> in an editorial in the *Journal of Surgery, Gynecology and Obstetrics*, stated "Most students of the pathology of acute cholecystitis now agree that obstruction to the cystic duct is the primary lesion in this disease, and that *infection, when it occurs in these cases, is a secondary phenomenon* which is dependent on this obstruction for its development." Also "Such patients reveal at operation tensely distended, edematous, red gallbladders. Yet their course following immediate cholecystectomy is generally very much like the course of any laparotomy for a non-inflammatory lesion." It has also been observed that when cultures are made of such gallbladders, they frequently are sterile. No doubt in many cases stones may be found impacted in the neck of the gallbladder or in the cystic duct, but not uncommonly no stones will be found and one at once must speculate upon the cause of the peculiar type of reaction. Judd likened it to a chemical process. Such an experience about ten years ago led me to suspect a pancreatic juice reflux as a possible etiologic factor, and, in 1931, the results of experimental work were published.<sup>12</sup> In 1937, further observations and conclusions were given in a communication.<sup>13</sup> The details of the experiments and conclusions previously presented will be omitted in this communication, however, a few of the pertinent points will be mentioned to clarify the subject.

It was proved experimentally that pancreatic juice when introduced in the gallbladder of the dog invariably produced pathologic changes in the wall of the gallbladder. These varied from degenerative changes characterized by extensive necrosis to complete gangrene and regenerative changes, displaying inflammatory reaction with interstitial, lymphoid and papillary hyperplasia. It was also shown that India ink which had been introduced into the terminal end of the common duct of the dog was later recovered in the gallbladder. Evidence was presented to show that known and unknown factors are present which may activate the pancreatic juice, and that the degree and nature of the alteration in the wall of the gallbladder may depend upon a degree of activation and dilution of the pancreatic juice, stasis most likely being an essential factor. Attention was also called to the frequency of an anatomically proven common pathway between the pancreatic and biliary tracts.

It is the purpose of this communication to further elaborate upon phases

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of the theory that pancreatic juice reflux may be an etiologic factor in gall-bladder disease

It has been proved by anatomic study that in a fairly large percentage of cases a common pathway between the pancreatic and biliary passages is present, allowing a reflux of the pancreatic juice into the biliary ducts. A compilation of statistics from eight authors reporting upon examinations of 652 speci-

TABLE I

Author	Total Number	Number with Common Pathway	Per Cent
Opie	100	11	11
Baldwin	90	20	22
Schirmer	48	22	47
Belou	50	27	54
Ruge	43	32	75
Letulle and Nattan Larrier	21	8	38
Cameron and Noble	100	74	74
Mann and Giodano	200	90	45
	652	284	43.4

mens shows a common pathway in 284 instances, or 43.4 per cent (Table I). The question may be raised as to whether in the living a common pathway is physiologically present. Cholangiography, or radiologic visualization of the biliary tree after the introduction of an opaque material, has been developed to a marked degree during the past few years. In studying these cholangiograms, it is noted that in quite a number of instances the pancreatic duct is visualized and in the presence of obstruction at the papilla, the pancreatic duct may be dilated (Figs. 1 and 2). Our series is too small to report at the present time, however, we have noted visualization of the pancreatic duct, and in studying cholangiograms which have appeared in current articles and in private collections, its presence has been detected. Doubilet and Colp<sup>4, 5</sup> have recently reported that in a series of 22 cases in which common duct drainage was instituted, eight cases showed significant to large amounts of amylase in the duct drainage, in fact, one case for a brief period of time drained almost pure pancreatic juice from the common duct. They also report that in all cases with common duct drainage in which the pancreatic duct could be visualized radiologically considerable quantities of amylase were found in the drainage from the ducts. There seems to be sufficient material available to warrant the conclusion that frequently a physiologic common pathway is present between the pancreatic and biliary ducts and that there is present in such instances a reflux of pancreatic juice into the biliary tract.

It may be postulated without fear of criticism that if a stone is impacted at the ampulla, and if the stone does not obstruct the orifice of the pancreatic duct in the presence of a common pathway, pancreatic juice may mix with the biliary contents of the common duct, and finally reach the gallbladder. It is a fact that stone impaction at the ampulla is uncommon in the average case of

cholecystitis, however, surgeons are reporting increasing numbers of instances of stones in the common duct when operating for cholecystitis, Lahey recently placing the figure at 21 per cent. Free stones in the common duct afford an excellent opportunity for temporary occlusion at the sphincter, or their presence may cause a low grade papillitis with a spasm of the sphincter. However, to prove the thesis, one must look further for a cause for obstruction, one which precedes the formation of stones.

FIG 1

FIG 2

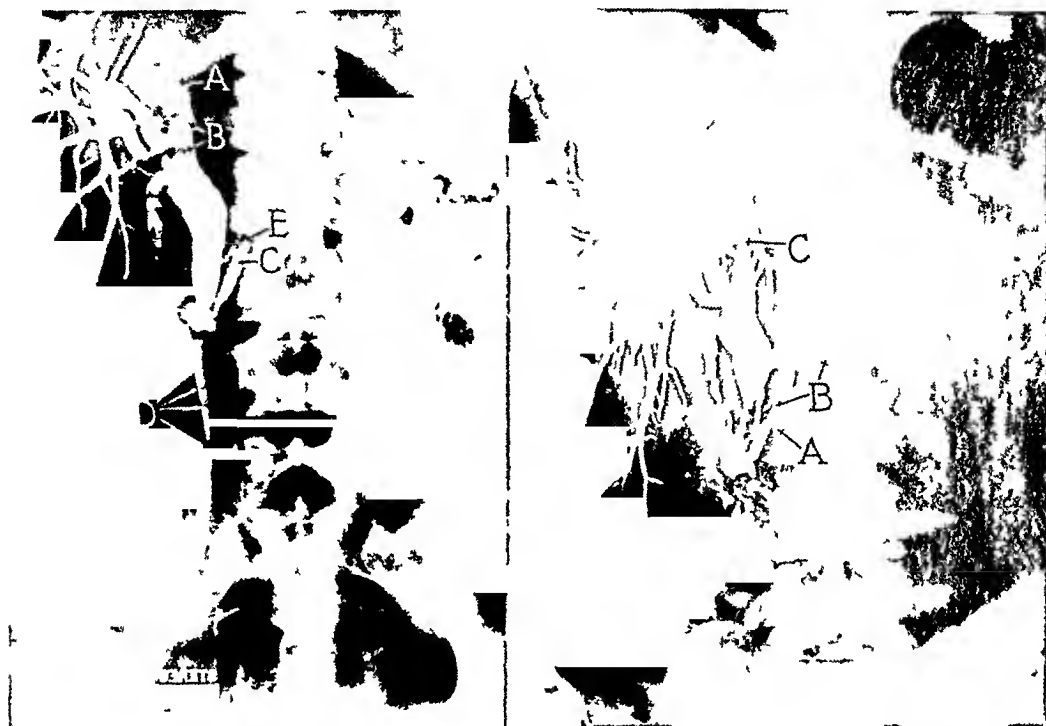


FIG 1—Cholangiogram made after the removal of common duct stones. Anteroposterior position. (A) Abrupt ending of the left hepatic duct as if obstructed. (B) Vacuoles which resemble those produced by stones. (C) Pancreatic duct. (D) Air globules in the catheter. (E) Constriction in the pancreatic duct which may be due to spasm.

FIG 2—Cholangiogram of same patient as in FIG 1 taken in the posteroanterior position about five minutes later. (A) Accessory pancreatic duct. (B) Pancreatic duct showing the median portion more distended than the terminal due either to spasm of the duct or organic stenosis. (C) Left hepatic duct well visualized. (It will be noted that the vacuoles shown in FIG 1 are no longer present, demonstrating sources of error in the technic of cholangiography and in the interpretation of cholangiograms. The vacuoles in FIG 1 were caused either by localized accumulations of duct contents which did not fuse with the oil suspension, or by air. The presence of air in the catheter in FIG 1 is evidence that air was being introduced. The abrupt ending of the left hepatic duct in FIG 1 may be due to position since a change in position was followed by an immediate filling.)

It is conceded by all physiologic investigators that a true sphincter is present at the terminal end of the common duct, also that there is a normal or physiologic mechanism which controls the evacuation of the bile as it is secreted by the liver. It is further presumed that a sphincter or some sphincteric action is necessary for the gallbladder to fill and allow it to concentrate its contents, and eventually to expel it into the common duct and subsequently into the duodenum. The normal mechanism is believed to be that when the gallbladder contracts, the sphincter relaxes. There may be variations in this mechanism. It is common knowledge that following cholecystectomy, the sphincter becomes incompetent, the intraductal pressure falls, and there is

more or less continuous flow of bile into the duodenum during digestion. This would indicate that there is a close physiologic relationship between the gallbladder and the sphincter. The sphincter is responsive to various drugs. Hunt, Hicken, and Best<sup>8</sup> and Doubilet have shown that morphine causes marked and continuous spasm of the sphincter. Doubilet and Colp have shown that the instillation of dilute hydrochloric acid into the duodenum brought about a prompt rise in the intraductal pressure, and that the instillation of a magnesium sulphate solution caused a fall in the pressure. They have also proved that the spasm produced by the instillation of dilute hydrochloric acid into the duodenum can be abolished by atropine. These experiments indicate that the sphincter is susceptible to various influences. Ivy<sup>9</sup> states that any condition which increases the tone of the duodenum retards the flow of bile into the duodenum, and that which decreases the tone of the duodenum and promotes normal peristalsis favors the flow of bile into the duodenum. There is sufficient evidence to prove that there are variations in the sphincter mechanism which are at variance with the normal and lead to biliary stasis. Ivy has reported one such case—a patient with previously normal cholecystogram and normal roentgenologic findings in the alimentary tract suffered from acute right upper abdominal and epigastric distress, and mild icterus with an enlarged tender gallbladder. The patient reported feeling a tumor in the region of the gallbladder. Five to ten minutes after the hypodermic injection of 1/60 gr. of atropine, the distress and tumor disappeared, and several hours later, a stool consisting of almost pure dilute bile was evacuated. It is evident that this disturbance or dissociation in the biliary motor mechanism, termed biliary dyskinesia or dyssynergia, is sufficient to produce symptoms, and may supply the mechanism for pancreatic juice reflux in the presence of a common pathway.

It has been shown by us that India ink which was introduced into the terminal end of the common duct of the dog was later recovered in the gallbladder. The question may arise as to the mechanism involved. Ivy has stated that the gallbladder "is a reservoir of small volume but of large capacity." Under normal conditions, it may concentrate its contents 10 to 1. In the presence of an obstruction at the papilla, be it organic or functional, the pressure within the common duct increases. Since the pancreatic juice is under higher secretory pressure than the bile, the level of pancreatic juice in the common duct will ascend toward the liver. During this time the contents of the gallbladder are being concentrated, allowing more common duct contents to enter. It is but a matter of time until pancreatic juice enters the gallbladder.

The agent which activates the pancreatic juice is still not definitely determined. Since the gallbladder is an offshoot from the intestinal tract, embryologically, it is believed by some that its mucosa secretes enterokinase. If this is true, the amount is exceedingly small. It is known, however, that substances other than enterokinase may activate pancreatic enzymes. This problem was discussed in some detail in a previous communication. It has been proved that

normal bile will not activate pancreatic juice (Doubilet), also it has been shown that a substance liberated by broken down cells may act as an activating agent (Lombardi). Lombardi,<sup>11</sup> Dragstedt<sup>7</sup> and others<sup>12 13</sup> have shown that sterile pancreatic juice is inactive, but that when it is contaminated, it becomes active, Lombardi believing that the activating substance is derived from the micro-organism. He has termed this substance bacteriokinase. Ivy<sup>10</sup> noted a violent reaction of the mucosa of the gallbladder after the introduction of 15 cc of 1/10 normal sodium bicarbonate solution into the gallbladder. Since pancreatic juice has approximately the same degree of alkalinity as 1/10 normal sodium bicarbonate solution, it may be reasoned that the alkaline pancreatic juice when it comes in contact with the gallbladder in sufficient quantity and concentration may produce a chemical irritation of the mucosa with destruction of cells. A specific substance liberated by the disintegrated cells then activates the pancreatic enzymes. Other factors may be present as proposed by Lombardi.

The relative infrequency of involvement of the walls of the common duct was explained by Brackertz<sup>1</sup> to be due to an inordinate amount of elastic tissue beneath the mucosa. This theory cannot be accepted since elastic tissue beneath the mucosa would not protect the mucosa against the digestive action of activated pancreatic juice. The explanation is most likely on the basis of an increased resistance of the mucosa to an alkaline medium, since the liver bile is alkaline, constant dilution of the pancreatic juice by liver bile and the lack of stasis or prolonged and continuous contact.

Observations during the past few years lead to the conclusion that many cases of cholecystitis as well as common duct and gallbladder stones can be accounted for on the basis of a pancreatic juice reflux. It is suggested that consideration be given to endocholedochal section of the sphincter of Oddi described by Colp, Doubilet and Gerber<sup>3</sup> as a possible form of treatment in some cases.

With the pancreatic juice reflux theory of the causation of gallbladder disease in mind, it is recommended that some widespread observations be carried out:

- (1) Repeated examinations for amylase should be made of the drainage in all cases of gallbladder and common duct drainage.
- (2) In all cases of gallbladder and common duct drainage, cholangiographic studies should be made in an endeavor to visualize the pancreatic duct.
- (3) In all cases of gallbladder and duct disease, note should be taken of the possibility of an early history suggestive of biliary dyskinesia.

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## A STUDY OF THE RESULTS OF SURGICAL TREATMENT OF PEPTIC ULCER

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A FOLLOW-UP CLINIC was organized in the Surgical Department of the Presbyterian Hospital in 1916 For the past 22 years, the Senior members of the staff, with their associates, have spent one full morning each week in this clinic, studying and recording the results of surgical therapy As a result of the clinic, the intimate relationship between doctor and patient has deepened with time

An idea of the effort made by the surgeons and clinic aides, and of the resulting response made by the patients in a large metropolitan community, is gained from the following figures namely, in the year 1935, 5,983 patients were asked to return to the general Surgical Follow-Up Clinic, of these, 5,034 did return, 883 responded by letter, and only 66, or about 1 per cent, were lost It is only by such high incidence of interviews between doctor and patient, months or years after operation, that accuracy in the estimation of the results of therapy can be approximated

The follow-up visits in many types of cases are discontinued after a reasonable length of time In the special clinic for the study of peptic ulcer, however, as in certain other types of cases, no case is discontinued, hence follow-up studies are possible over long periods of time Of equal importance, we believe, is the fact that each case is followed in continuity, that is, the continuous postoperative course is charted rather than just the clinical, symptomatic picture at stated intervals For convenience these records are maintained graphically

A standard method for recording follow-up results must, of course, be agreed upon in any such study The method in use in our clinic gives the result from anatomic, symptomatic and economic standpoints In the present study of peptic ulcer the symptomatic results, only, are under consideration There are four main groups into which all results are divided Groups 4 and 3, which form the satisfactory ones, and Groups 2 and 1, the unsatisfactory Group 4 includes only the cases with no symptoms whatever at any time since operation Group 3 includes only cases with no significant symptoms, or in other words a very satisfactory group, in which only the mild digestive disturbances to which normal man is heir may occur

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Groups 2 and 1 include all unsatisfactory cases, Group 1 representing the least satisfactory results of all, including the failures. In addition, for purposes of this critical review, in a given case, if an unsatisfactory record is noted at any time during the postoperative course, then this case is *permanently* dropped from the satisfactory groups, as will be seen later.

The purpose of this study was to review individually, and as a group, the cases which had passed through our hands, in order to obtain, if possible, a foundation upon which to base the treatment of new cases in the future. We had found that none of us was consistent in his recommendations for therapy, largely because, as a group, we did not know accurately the results of our recommendations in the past. In the 20-year period which this study covers, some of our patients had improved after operation. In others, the benefit was doubtful or clearly absent. By a careful appraisal of the follow-up records we hoped to be able to separate, with reasonable accuracy, the individuals that had been treated successfully from those that had not. If, then, we could find a set of factors peculiar to the successful or unsuccessful groups, we might obtain standards to guide us in selecting cases for operation and in choosing which type of operation to employ for individual cases.

Statistics derived from the study of groups are notably unreliable as a basis for the treatment of any individual, and it is always an individual for whom one must make recommendations. In this study, however, we have had the advantage of knowing well almost every patient within the group, so that we have been able to consider the records on the charts in the light of what we knew from contact with the patients themselves, in a way that an independent reviewer could not do. If the record seemed misleading, we could verify or correct it. In this way, some of the dangers inherent in dividing patients into artificial groups could be minimized.

The cases included in this study are all those who were operated upon at the Presbyterian Hospital for gastric or duodenal ulcer, between the years 1916 and 1935 inclusive, excepting the few that were operated upon elsewhere, previously. They, therefore, include the patients of some 25 surgeons. No one technic was followed. After operation, all patients, with the few exceptions noted in the tables, were seen at follow-up visits in the clinic or privately, at which times they were questioned as to their symptoms since their previous visits, examined, and frequently roentgenographed. They were then rated at each visit anatomically, symptomatically, and economically on the basis used in our Follow-Up Clinic and explained above. As noted before, it is the symptomatic rating with which this study is concerned.

In 1935 and 1936, the records from the charts were transferred to cards, samples of which are herewith reproduced. The cards have advantages in filing and reviewing that the charts cannot have. They furnish graphically, and at a glance, the important details of histories which may be of many years' duration. Anyone who has struggled through a voluminous record, attempt-

ing to get a conception of the case as a whole, will appreciate the value of these cards as adjuncts to the charts. From the cards and the charts and our knowledge of the patients themselves, we have compiled the accompanying tables.

We have used certain terms in the tables that need definition. We have included under gastric ulcer only those ulcers that did not directly involve the duodenum. Most of these were of the familiar lesser curvature kind. All other ulcers we have called duodenal, whether they were clearly in the duodenum, or in the pylorus, or spread out into both. The criteria have been explained for rating the cases as symptomatic Group 4, 3, 2 or 1. Groups 4 and 3 represent the satisfactory results, Groups 2 and 1 the unsatisfactory. Where the information was not obtainable as to rating, we have used the term "Insufficient Follow-Up." This does not mean, of course, that we consider the follow-up on all other cases "sufficient," but merely that we have enough information about them to rate them with confidence, as of the date of this report. In postoperative deaths, we have included all cases that died in the hospital following operation, whether the death was thought to be due directly or indirectly to the operative procedure. Only one other patient, who died at home three months after leaving the hospital, could in reason be added to this list.

Finally, in some tables we have divided the cases into those showing before operation (1) Obstruction, (2) Bleeding, or (3) Pain, as the outstanding symptom. Under Obstruction are those cases which had 50 per cent or more six-hour retention, or any 24-hour retention determined roentgenologically, with the added provision that this degree of retention had to be persistent and unrelieved at the time of operation. Under Bleeding we have placed those cases in which there was convincing evidence of gross hemorrhage at any time before operation. We did not include in this group the cases that had only occasional evidence of occult blood. Cases which had both obstruction and bleeding we have placed under Obstruction with the notation that they also bled. All cases having neither obstruction nor bleeding we placed under the heading Pain, as this was then outstanding symptom.

The separation of cases into these three groups—Obstruction, Bleeding, and Pain—can never be wholly accurate. Hemorrhages in some individuals may easily go unobserved. The degree of obstruction may vary, so that an individual meeting the standards of the Obstruction group at one period might fail to meet them at another. Conceding all this, it is nevertheless true, as the tables show, that the groups so chosen responded differently to forms of therapy, notably to gastro-enterostomy, so that it is now possible to select with greater assurance the individuals upon whom to perform this operation, and equally important to discontinue its use in cases comparable to those in which it has proven unsatisfactory. The justification for the

grouping, therefore, lies in the aid it should give in the management of future cases

In appraising the operative result in each case, we have raised two questions. First, has the individual *at any time* since his operation had significant symptoms of ulcer, and second, in how many *years* since his operation has he had such symptoms? The answers to the first we have noted under "Results According to Cases," and to the second under "Results According to Years." According to the first standard, if an individual in a single instance had symptoms which caused him to be rated as unsatisfactory, he was then, forever, classed as unsatisfactory, because it is clear that the operation did not rid him of his disease. But the same individual may have been wholly free of symptoms for many years before and after his single fall from grace. It is unfair not to distinguish him from the patient, who, year after year, showed no benefit from operation. The tables showing the "Results According to Years" take account of this difference. The case of B F, Charts No. 5 and 6, a facsimile of whose record is given below illustrates this point. For eight years, B F came to the Follow-Up Clinic, the picture of health, denying any symptoms of gastro-intestinal distress, although before operation, for four years, he was rarely free of pain. He then appeared almost in collapse as the result of a severe hemorrhage which might well have been fatal. How much benefit from operation had he? Much, according to years, as a "cure," none. While he is an extreme example, he demonstrates the difficulty of estimating fairly the results of therapy in this variable disease, and the need for adopting more than one standard of judgment. In general, even reading the two sets of tables together, a conception of the results of surgery is obtained which may be unduly pessimistic. Many of the patients that we have labelled "unsatisfactory," when asked whether they have received benefit from the operation, reply with conviction, "Yes." Lacking acquaintance with them over the years before operation, as intimately as we have known them after, it is impossible for us to know whether to agree with them.

The analysis of the ulcer cases in the manner described above has done much to fulfill its purpose. Faced with a new patient, we may now state, with fair assurance, into what group he falls, *i e.*, Obstruction, Bleeding or Pain. In addition, we believe that we can advise more intelligently the operative procedure indicated in his case. Also, we venture to say that we can tell him with greater accuracy what the result of the operation will be. Finally, if the conclusions based upon this study are correct, our future results should show a distinct improvement.

But we are still lacking information as to what result may be expected in case we do not operate, because, so far as we know, no large group of medically treated cases has been carefully followed over a long period of time. The choice between operating or not upon each patient is, to that

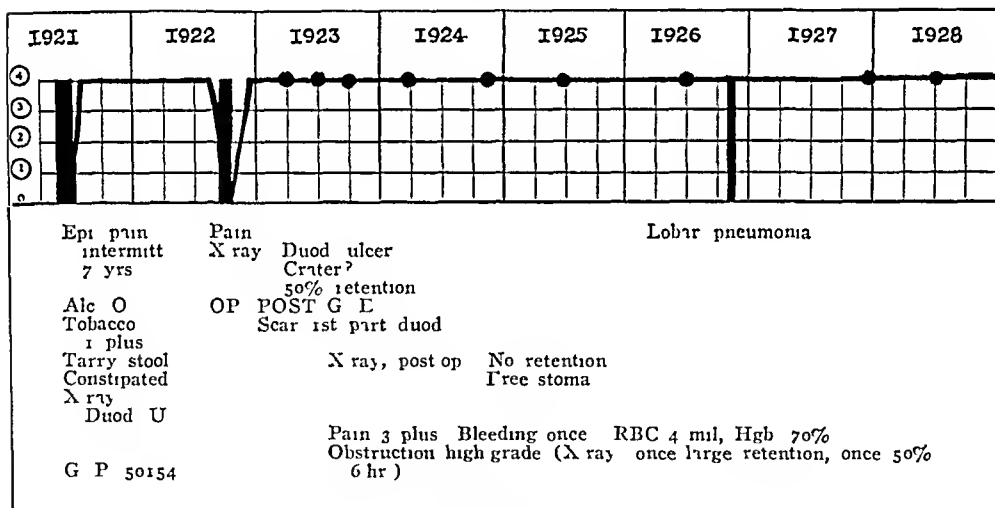
serious degree, made difficult. We are beginning, however, to correct this fault. For the past five years, a Medical Follow-Up Clinic, comparable to the Surgical Follow-Up Clinic, has existed for all the cases treated medically in the wards of the Presbyterian Hospital. While this period of observation is short, it is sufficient to indicate that almost all of the patients so treated become unsatisfactory at some time after leaving the hospital, and that at any given time approximately one-fourth of them are unsatisfactory. These two observations form a basis of comparison, respectively, for the surgical "Results According to Cases" and "Results According to Years." It is not a good basis, because many of the medically treated cases are milder than those operated upon, but it has some value. We do not yet know how many of these patients will die of their ulcers over the years, as a point of comparison with the postoperative and late death rate of the surgically treated patients, but we do know that the medical mortality is a real one, as some of the medically treated cases have already died of hemorrhage or perforation since leaving the hospital. In ignorance of so much that we need to know, we have adopted the policy of considering surgery only for individuals who have not responded favorably to one or more thorough courses of medical regimen including rest in bed. Some day, perhaps, it will be possible to select cases for operation without subjecting them to such courses, which are always prolonged and sometimes futile. From the records of the Medical Follow-Up Clinic, five or ten years from now, may well come information that will enable us to predict which cases are apt to do well under medical treatment and which cases not. Early operation on the latter would save not only time but lives as well, which now are lost by hemorrhages, perforations, or postponement of operation until the disease is associated with serious complications or the patient is debilitated by illness or has reached advanced years.

Another question to consider in appraising the results of any form of therapy for ulcer is: To what degree of freedom from symptoms are we aiming to bring the patients? Are we to be content only with complete freedom from digestive disturbances, or may we be satisfied if they achieve the digestive status of people without ulcers? If the latter, what is that status? In order to gain some answer to the last question, we interviewed 100 patients in the Fracture Follow-Up Clinic, all of whom had been hospitalized for fractures, and whose residence, age and economic level were roughly comparable to those of our ulcer cases. The questions asked of them were the ones asked in the Ulcer Follow-Up Clinic, and the individuals were rated according to their symptoms in the same manner as in the Ulcer Clinic. As a result of an analysis of this study, 81 per cent were classified as satisfactory and 19 per cent as unsatisfactory. In those that had symptoms, worry and fatigue were recognized as the usual predisposing factors. While this study comes far from setting a standard, it does agree with the common knowledge that somewhere around 10 to 20 per cent of people will have

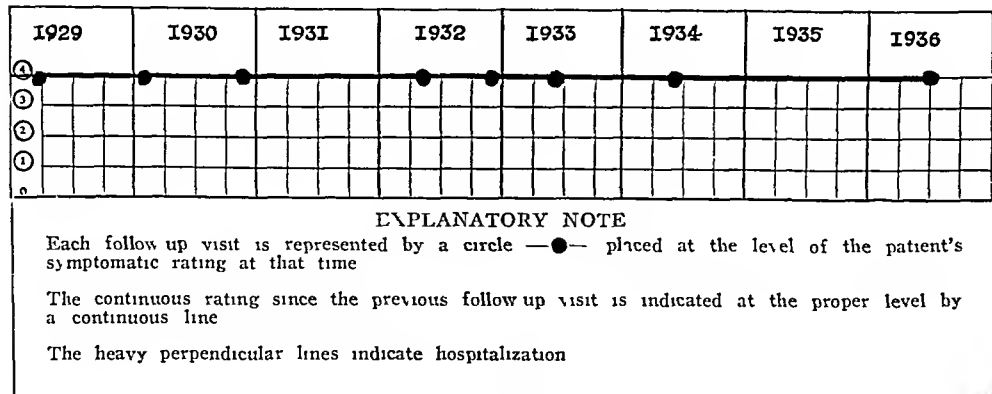
### CHART 1

Name	Mr. G. P	Age	30	Sex	Male	Race	Negro	Serial No	----
Address	436 Convent Avenue Apartment 36 New York City	Religion	Prot.	Unit No	50154	Surg Path No	-----		
		Birthplace	B W I	X Ray No	7356	Attending Dr	X		
		Marital State	Married	Surgeon	Dr Y				
		Occupation	Porter						
		Personality	Pleasant-	well adjusted					
X Ray Diag	Ulcer of duodenum Localized tenderness and 50% 6-hr residue	Adm	May 9/1921.	Dis	May 28/1921	Remarks	Uncomplicated convalescence		
Discharge Diag	Ulcer of duodenum	Operation	Posterior gastroenterostomy, side of stomach to side of intestine, suture						

## CHART 2



### CHART 3



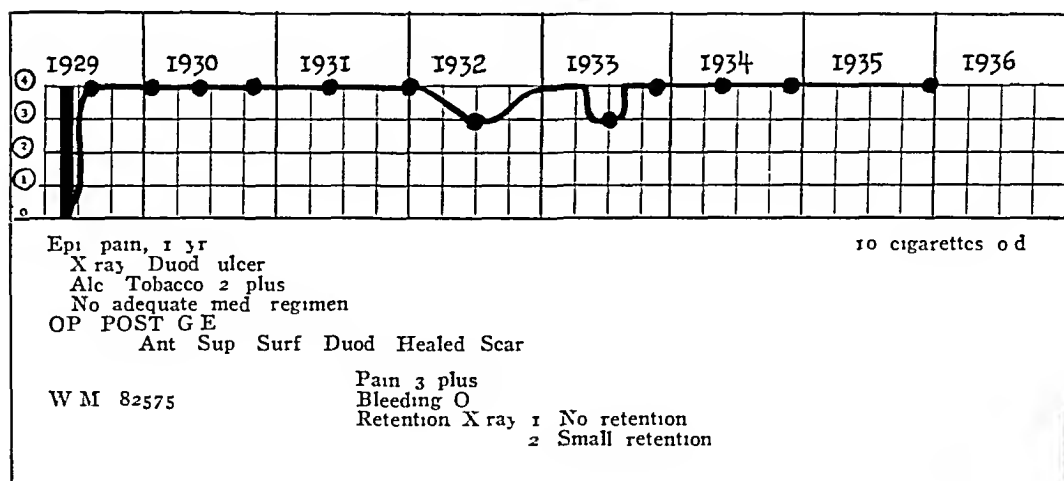
digestive symptoms of more than mild degree without demonstrable ulcers and that from time to time digestive complaints will appear among ulcer patients even if their ulcers are healed

We are only too well aware of the part played by emotional stress and strain, instability and real psychopathic conditions in this disease, but have lacked the opportunity of studying this phase of the problem as it should be studied Suffice it to say that this factor colors the results to be reported

A glance at several illustrative cards will make more clear the type of individual records that form the basis for the summaries printed in the tables G P, Charts No 1, 2 and 3, was treated in the hospital in 1921 for symptoms of duodenal ulcer of seven years' duration The symptoms recurred a year later, and posterior gastro-enterostomy was performed He had six-hour retention, roentgenologically, in 1921 (amount not stated), and 50 per cent retention again, in 1922, before operation, with evidence of ulcer at both observations He also had severe pain and gross bleeding During almost 14 years of postoperative visits, he has admitted no distress He is accordingly classed as Duodenal Ulcer with Obstruction and Hemorrhage, posterior gastro-enterostomy, Group 4 in the tables of "Results According to Cases," with 14 Group 4-years in the tables of "Results According to Years"

W M, Chart 4, illustrates Duodenal Ulcer with Pain, because he had no high-grade persistent obstruction and no gross bleeding In the "Results According to Cases," he appears as Group 3, because he complained of mild symptoms at a follow-up visit (on two occasions in this instance) In the "Results According to Years," he has four Group 4-years and two Group 3-years to his credit This case and the one preceding are considered satisfactory, because they have never had severe postoperative symptoms

CHART 4



B F, Charts 5 and 6, represents a Duodenal Ulcer with Pain, who, after three years of pretty constant distress, was treated in the hospital in 1924 He had recurrence of symptoms in 1925, for which Gastro-enterostomy was done After more than eight years in which he admitted no symptoms, he suffered a severe hemorrhage and recurrence of ulcer pain He is rated in

Results According to Cases as Group 2, Unsatisfactory, with, however, eight Group 4-years and one Group 1-year in Results According to Years

CHART 5

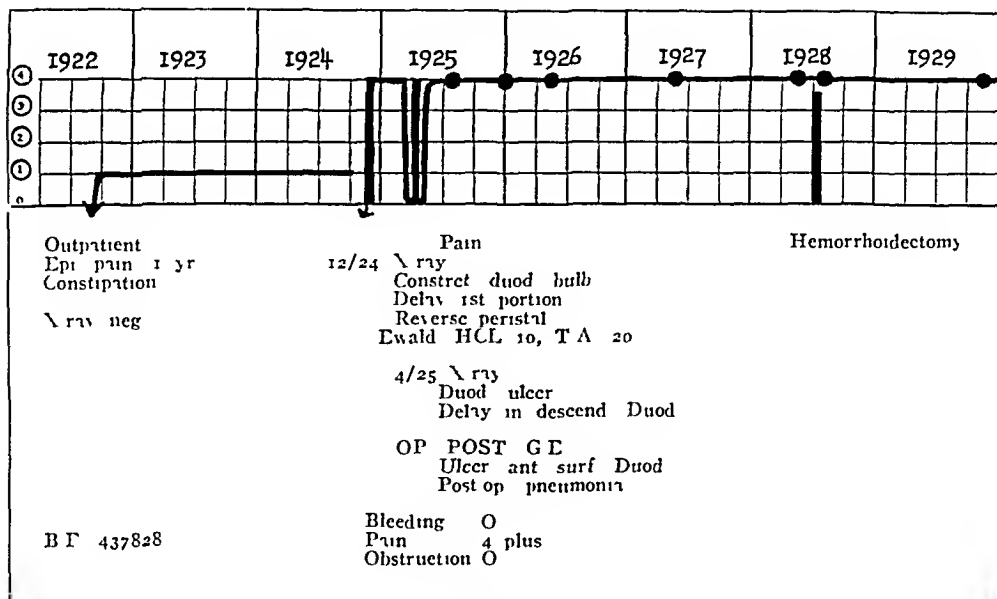
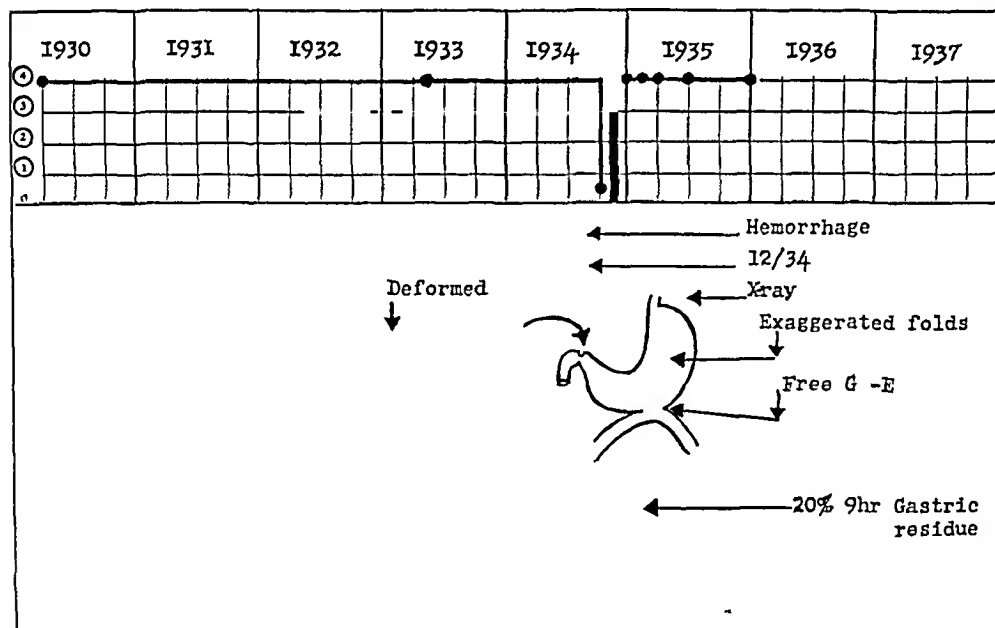


CHART 6



J H, Charts 7 and 8, after a Finney type of pyloroplasty, is rated as a Group 1, unsatisfactory, in "Results According to Cases," because of his experiences in 1929 and 1932, although for the first ten years his complaints were few. He has six Group 4-years, four Group 3-years, two Group 2-years and three Group 1-years.

PEPTIC ULCER

CHART 7

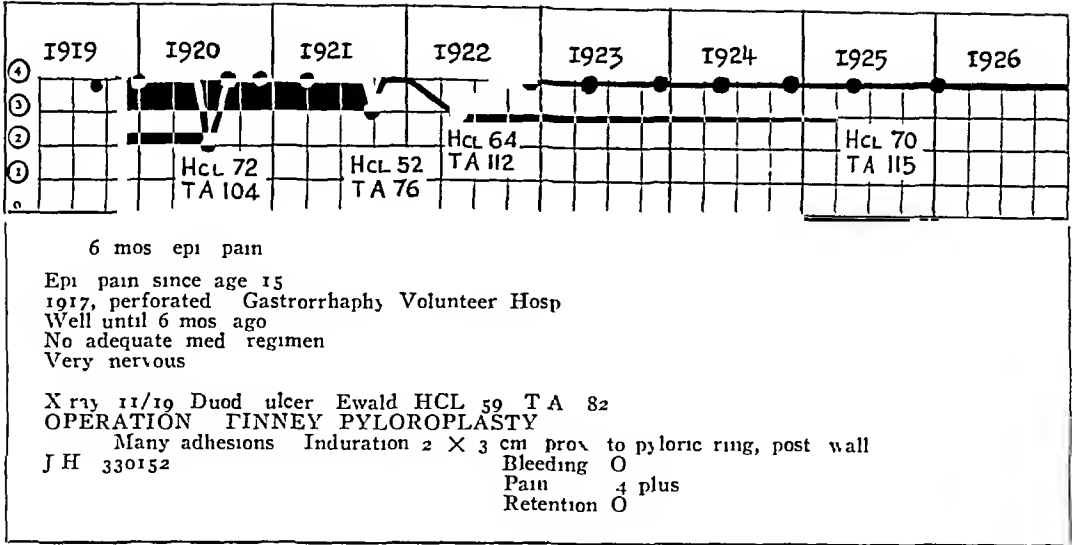
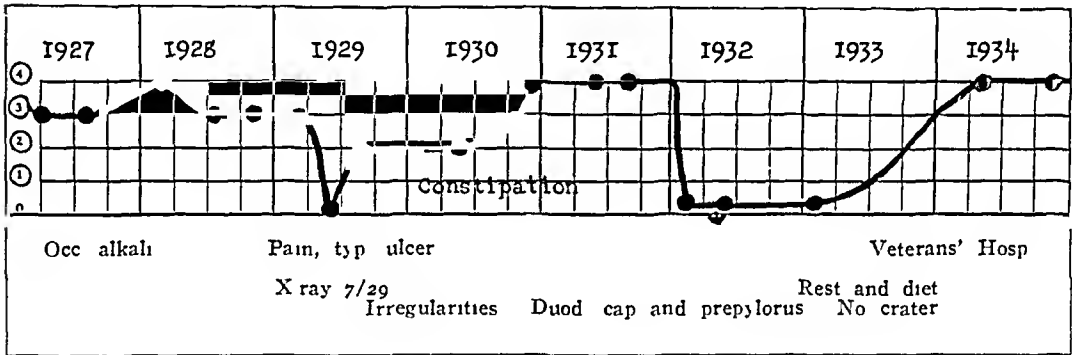


CHART 8



Not all cases were so easy to classify as the ones just cited, but the difficult ones were not numerous. Having assembled our information regarding each individual, it was then possible to arrange the cases into groups and so construct the tables. For completeness, these tables include all our cases, and so contain many figures that are not of great significance. Where the figures seem of special interest, they are printed in bold-faced type.

Table I affords a comparison of the results of various operations for duodenal ulcer, according to cases. The gastro-enterostomies are divided into three groups, performed in individuals, who, before operation, had obstruction, hemorrhage or pain. This division is not made for the other operations, because in the partial gastrectomies the difference in results among the three groups is not marked, and in the other operations the number of cases is not large enough to divide. It is to be noted that in the Obstruction group, proportionately about twice as many individuals remained always satisfactory as in the Hemorrhage or Pain groups. This is shown in the column headed "Satisfactory Survivors." It is true that the average follow-up for the Obstruction group is a little shorter, but not enough to account for this striking difference. In the same column, it also appears that the results after partial gastrectomy are far better



TABLE I  
DUODENAL ULCER  
FOLLOW-UP RESULTS ACCORDING TO CASES

Type of Operation	Total Cases	P O Deaths	Insuff Follow-Up	Followed Survivors	Satisfactory Survivors	Unsatisfactory Survivors	Group				Average Follow-Up Years
							4	3	2	1	
Post gastro-enterostomy Obstruction group	70 (14)*	7 (2) 10% 14%	0	63 (14)	51 (11) 81% 79%	12 (3) 19% 21%	36 (7)	15 (4)	3 (1)	9 (2)	5 4
Post gastro enterostomy Hemorrhage group	46	7 15%	7	32	13 41%	19 59%	8	5	3	16	6 3
Post gastro enterostomy Pain group	109	9 8%	11	89	39 44%	50 56%	22	17	24	26	6 3
Totals	225	23 10%	18	184	103 56%	81 44%	66	37	30	51	
Partial gastrectomy a Billroth II 35 Polya 37	72	13 18%	4	55	42 76%	13 24%	28	14	7	6	4 3
b Billroth I 6 Moynihan 3	9	2 22%	0	7	3 43%	4 57%	3	0	3	1	5 0†
Pyloroplasty a Finney type	13	1 8%	2	10	7 70%	3 30%	5	2	2	1	3 3‡
b Horsley type	11	0	0	11	6 55%	5 45%	4	2	2	3	4 6
Excision or cauterization plus gastro enterostomy	10	0	1	9	4 44%	5 56%	4	0	2	3	5 0§
Miscellaneous	15	8 53%	2	5	1 20%	4 80%	0	1	2	2	4 8
Totals	355	47	27	281	166	115	110	56	48	67	

\* Figures in parentheses refer to the number of bleeders in the obstruction cases

† Satisfactory cases followed only one year each

‡ Only two satisfactory cases followed over two years

§ Three of the four satisfactory survivors were obstruction cases.

TABLE II  
DUODENAL ULCER  
FOLLOW-UP RESULTS ACCORDING TO YEARS

Type of Operation	Total Years	Satis- factory Years	Unsatis- factory Years	Symptomatic Group				Deaths from Ulcer	Deaths from Other Causes
				Four	Three	Two	One		
Post gastro enterostomy	346	314	91%	32	9%				
Obstruction group				Yrs	Yrs	Yrs	Yrs		
Post gastro enterostomy	201	161	80%	277	37	12	20		
Hemorrhage group									
Post gastro enterostomy	575	438	76%	108	53	11	29	1	6
Pain group									
Totals	1,122	913	81%	311	127	46	91	2	4*
Partial gastrectomy									
a Billroth II and Polva types	230	195	85%	696	217	69	140	1	8
b Billroth I and Moynihan	35	27	77%						
Pyloroplasty									
a Finney type	35	27	77%	35	15%				
b Horsley type	33	28	85%	8	23%				
Excision or eauterization of ulcer	46	39	85%	22	27	19	16	4	18
plus gastro enterostomy	45	32	71%	5	5	4	1	1	
Miscellaneous									
	24	14	68%	20	8	1	0	0	3
				24	15	1	4	1*	
Totals	1,535	1,248		29	3	2	5	0	0
				10	32%	5	8	0	0
* One from lung condition developing postoperative			287	9	4	6	1	0	0
				964	284	104	183	7	22

than after gastro-enterostomy when the latter is performed for hemorrhage or pain. For the Obstruction group alone, partial gastrectomy has given no better results than gastro-enterostomy, and the death rate for the latter is less. The Finney type of pyloroplasty has the third best results, but this statement is made with the important reservation that only two of the seven satisfactory cases in this group have been followed for more than two years. The death rates are discussed below.

Table II gives the same comparison as Table I, but based on follow-up-years instead of cases. In this table, each year is counted at the lowest symptomatic rating to which the patient fell at any time during that year. The results of gastro-enterostomy performed for the Obstruction group again lead, with only 9 per cent-years that contained at any time an unsatisfactory rating. Partial gastrectomy of the Billroth II or Polya types yielded 85 per cent satisfactory-years, better than gastro-enterostomies as a whole, but not so good as the gastro-enterostomies in the Obstruction group. The pyloroplasties also yielded 85 per cent satisfactory-years, but their total number of follow-up-years is small. The results in this table, therefore, parallel those in Table I. The difference between the two ways of judging the results appears in this fact. In Table I, only 59.1 per cent of all the cases remained satisfactory, whereas, in Table II, 81.3 per cent of all the follow-up-years were satisfactory.

In Table II also appears the interesting fact that seven of the 281 individuals that were followed died of their ulcer at some time after leaving the hospital. To these must be added two, who died of pulmonary lesions which developed shortly after operation, one of pulmonary tuberculosis which became active, and one of multiple lung abscesses. Twenty died of other causes.

Table III and Table IV give the same results as Tables I and II, but in relation to gastric ulcer instead of to duodenal ulcer. There is no question but that for gastric ulcer, partial gastrectomy of the Billroth II or Polya types has been the procedure of choice, with 90 per cent of the survivors satisfactory when grouped according to cases (Table III), and 92 per cent satisfactory-years (Table IV). Few major surgical procedures for any lesion would have so good a record. The postoperative death rates are discussed below. Gastro-enterostomies as a group did poorly. Four of the 70 followed survivors in the entire gastric group died of their ulcer after leaving the hospital. Of these deaths, three occurred among the 13 gastro-enterostomies. From these results, it is plain that gastro-enterostomy for gastric ulcer is contraindicated, but that an adequate partial gastrectomy offers real hope of cure. Actually, only two of the 31 followed survivors of partial gastrectomy have had recurrence of ulcer symptoms, as one of the three listed as unsatisfactory was so classified because he died of pulmonary tuberculosis activated by the operation.

PEPTIC ULCER

TABLE III  
GASTRIC ULCER  
FOLLOW-UP RESULTS ACCORDING TO CASES

Type of Operation		Total Cases	Postop Deaths	Insuff Follow-Up	Followed Survivors	Sats-factory Survivors	Unsats-factory Survivors	Group					Average Follow-Up	
Partial gastrectomy														
a Billroth II and Polya														
b Sleeve		13	37	3	3	31	28	90%	3*	10%	20	8	1	2
Billroth I		1	15	4	0	11	5	45%	6	55%	0	5	3	3
Moynihan		1	13	0	0	11	5	45%	6	55%	0	5	3	3
Posterior gastro-enter		9	16	2†	4	10	7	70%	3†	30%	3	4	0	3
Excisions		4	16	0	0	13	3	23%	10	77%	3	0	4	6
Cauterizations		3	7	0	0	5	2	40%	3	60%	0	2	2	1
Pyloroplasties		3	7	0	0	5	2	40%	3	60%	0	2	2	1
Miscellaneous		7	88	2	11	7	25	60%	0	2	2	1	5	7
Totals		88	11	0	7	45	25	60%	0	2	2	1	5	7
* One Tbc death														
† Both deaths in excisions														
† Unsatisfactory 2 pyloroplasties, 1 excision														

Type of Operation	Total Cases	Postop Deaths	Insuff Follow-Up	Followed Survivors	Sats-factory Survivors	Unsats-factory Survivors	Group					Average Follow-Up	
Partial gastrectomy													
a Billroth II and Polya													
b Sleeve	13	37	3	3	31	28	90%	3*	10%	20	8	1	2
Billroth I	1	15	4	0	11	5	45%	6	55%	0	5	3	3
Moynihan	1	13	0	0	11	5	45%	6	55%	0	5	3	3
Posterior gastro-enter	9	16	2†	4	10	7	70%	3†	30%	3	4	0	3
Excisions	4	16	0	0	13	3	23%	10	77%	3	0	4	6
Cauterizations	3	7	0	0	5	2	40%	3	60%	0	2	2	1
Pyloroplasties	3	7	0	0	5	2	40%	3	60%	0	2	2	1
Miscellaneous	7	88	2	11	7	25	60%	0	2	2	1	5	7
Totals	88	11	0	7	45	25	60%	0	2	2	1	5	7
* One Tbc death													
† Both deaths in excisions													
† Unsatisfactory 2 pyloroplasties, 1 excision													

TABLE IV  
GASTRIC ULCER  
FOLLOW-UP RESULTS ACCORDING TO YEARS

Type of Operation	Total Years	Sats-factory Years	Unsats-factory Years	Symptomatic Group					Deaths from Ulcer	Deaths from Other Causes
Partial gastrectomy										
a Billroth II and Polya										
b Sleeve, Billroth I and Moynihan	219	203	92%	16	8%	172	31	10	6	0
Excisions	93	74	80%	19	20%	48	26	12	7	0
Cauterizations	46	19	41%	27	59%	11	8	16	11	1
Pyloroplasties	76	60	79%	16	21%	46	14	7	9	0
Miscellaneous	40	33	83%	7	17%	5	28	1	6	0
Totals	474	389	85	282	107	46	39	4	0	0
* One death from tuberculosis										

TABLE V  
RESULTS ACCORDING TO CASES  
DUODENAL ULCER

	Satis- factory	Unsatis- factory	Satis- factory but Not Followed For Period Indicated	Became Unsatis- factory During Period Indicated
a Gastro enterostomy for obstruction				
At 3 yrs postop	40	6	17	6
At 5 yrs "	29	10	24	4
At 10 yrs "	11	11	41	1
At 15 yrs "	4	12	47	1
b Gastro enterostomy for bleeding				
At 3 yrs postop	17	10	5	10
At 5 yrs "	10	14	8	4
At 10 yrs "	5	18	9	4
At 15 yrs "	1	19	12	1
c Gastro enterostomy for pain				
At 3 yrs postop	46	35	8	35
At 5 yrs "	34	40	15	5
At 10 yrs "	13	46	30	6
At 15 yrs "	4	49	36	3
d Total gastro enterostomy				
At 3 yrs postop	103	51	30	51
At 5 yrs "	73	64	47	13
At 10 yrs "	29	75	80	11
At 15 yrs "	9	80	95	5
e Partial gastrectomy for duodenal and pyloric ulcers (Billroth II and Pólya types)				
At 3 yrs postop	29	9	17	9
At 5 yrs "	24	11	20	2
At 10 yrs "	13	13	29	2
At 15 yrs "	3	13	39	0
f Pyloroplasty for duodenal and py- loric ulcers				
Horsley type 11 cases				
Finney type 10 cases				
At 3 yrs postop	8	8	5	8
At 5 yrs "	2	9	10	1
At 10 yrs "	1	9	11	0
At 15 yrs "	0	9	12	0

## GASTRIC ULCER

a Partial gastrectomy (Billroth II and Pólya types)				
At 3 yrs postop	22	2	7	2
At 5 yrs "	18	2	11	0
At 10 yrs "	11	2	18	0
At 15 yrs "	2	3	26	1
b Pyloroplasties, excisions, cauteriza- tions				
At 3 yrs postop	6	2	2	2
At 5 yrs "	4	3	3	1
At 10 yrs "	2	4	4	1
At 15 yrs "	0	4	6	0
c Posterior gastro enterostomy				
At 3 yrs postop	2	9	2	9
At 5 yrs "	1	9	3	0
At 10 yrs "	0	10	3	1
At 15 yrs "	0	10	3	0

It is interesting to know how many individuals remained free of symptoms three, five, ten, and fifteen years after operation. Table V gives this information. In addition, it also shows the number of individuals who experienced their first recurrence of symptoms in each of the four given periods, *i e.*, in the first three years, between the third and fifth, and fifth and tenth, and the tenth and fifteenth years. It is a table compiled according to cases, that is, once an individual became unsatisfactory, even temporarily, he was thereafter classed as unsatisfactory. In the first group tabulated, the cases of duodenal ulcer with obstruction treated by gastro-enterostomy, it is seen that the 53 cases comprising this group were distributed as follows. After three years, 40 were still satisfactory, six had become unsatisfactory, and 17 were not yet followed for three years, but so far as they had gone were still satisfactory. At five years, four more had become unsatisfactory, so that the alignment then was 29 satisfactory, ten unsatisfactory, and 24 satisfactory but not followed the full five years. And so on for the tenth and fifteenth years. The results for the other groups of cases and after other operations may be similarly read. It is a difficult chart from which to draw deductions, because so many of the cases have not been followed for the full ten- or 15-year periods. It demonstrates, however, that a distressing number of initial recurrences of symptoms appear many years after operation. Of 29 cases free of symptoms after gastro-enterostomy for ten years, five had recurrences later, *i e.*, before 15 years. In the face of this, the publication of three- or five-year "cures" becomes meaningless.

Table VI has to do with the same cases included in Table V, but presents their postoperative records from the point of view of years instead of cases. It shows the number and proportion of the cases that were satisfactory during each postoperative year. This table, therefore, takes account of the good years and the bad years equally, without regard to how many years after operation the symptoms first recurred, or how many individuals remained free of symptoms for their whole postoperative course. The maze of numbers contained in the table is at first sight confusing, perhaps, but if the eye is allowed to travel down each column headed "Satis. Cases," the main significance of the figures becomes apparent. In the first place, it is interesting how little variation there is in any group in the proportion of cases who are free of symptoms in the various postoperative years. Secondly, it is seen that, among the groups, the obstruction cases with gastro-enterostomy (first group on the left-hand side) are almost uniformly over 90 per cent free of symptoms. The other groups are doing less well in almost every year. The difference becomes more striking if the columns showing "Unsat. Cases" are compared. In the years where the number of cases is small, the percentages lose meaning.

The findings in Tables V and VI agree in general with those in Tables I to IV, so far as the results of the various operations are concerned. Gastro-enterostomy for the obstruction cases has the best record, with partial gas-

TABLE VI  
RESULTS BY YEARS  
DUODENAL ULCER

Yrs P O	Posterior Gastro-enterostomy for										Total				Partial Gastrectomy, Billroth II and Polya				Pyloroplasties					
	Obstruction					Hemorrhage					Pain					Gastro-enterostomy								
	Satis Cases	Unsat Cases	Satis Cases	Unsat Cases	Satis Cases	Satis Cases	Unsat Cases	Satis Cases	Unsat Cases	Satis Cases	Satis Cases	Unsat Cases	Satis Cases	Unsat Cases	Satis Cases	Unsat Cases	Satis Cases	Unsat Cases	Satis Cases	Unsat Cases				
1	58	94%	4	6%	28	88%	4	12%	68	76%	22	24%	154	84%	30	16%	40	87%	6	13%	15	71%	6	29%
2	46	94%	3	6%	21	81%	5	19%	53	68%	25	32%	120	78%	33	22%	25	83%	5	17%	12	80%	3	20%
3	36	95%	2	5%	19	83%	4	17%	55	78%	16	22%	110	83%	22	17%	23	88%	3	12%	11	92%	1	8%
4	31	91%	3	9%	15	71%	6	29%	48	79%	13	21%	94	81%	22	19%	21	84%	4	16%	7	88%	1	12%
5	26	87%	4	13%	12	71%	5	29%	43	83%	9	17%	81	82%	18	18%	20	91%	2	9%	5	100%	0	0
6	23	92%	2	8%	11	85%	2	15%	32	76%	10	24%	66	83%	14	17%	17	81%	4	19%	5	100%	0	0
7	21	100%	0	0	8	67%	4	33%	28	80%	7	20%	57	84%	11	16%	16	84%	3	16%	4	80%	1	20%
8	18	100%	0	0	7	64%	4	36%	25	74%	9	26%	50	79%	13	21%	12	80%	3	20%	3	100%	0	0
9	12	80%	3	20%	7	78%	2	22%	26	81%	6	19%	45	80%	11	20%	12	92%	1	8%	2	100%	0	0
10	10	91%	1	9%	4	67%	2	33%	21	81%	5	19%	35	81%	8	19%	8	100%	0	0	2	100%	0	0
11	7	100%	0	0	4	67%	2	33%	14	74%	5	26%	25	78%	7	22%	4	80%	1	20%	0	0	0	0
12	7	100%	0	0	6	100%	0	0	6	55%	5	45%	19	80%	5	20%	0	0	2	0	0	0	0	0
13	7	100%	0	0	5	100%	0	0	5	63%	3	37%	17	85%	3	50%	1	50%	1	50%	0	0	0	0
14	4	80%	1	20%	4	100%	0	0	6	86%	1	14%	14	88%	2	12%	0	0	0	0	0	0	0	0
15	3	75%	1	25%	4	100%	0	0	3	75%	1	25%	10	83%	2	17%	0	0	0	0	0	0	0	0

trectomy almost equally good. The pyloroplasties, having so few cases, are difficult to judge, but do not seem to do as well as following the operations just mentioned. In reading these two tables it is helpful to bear in mind that so far as the study of the results of medical treatment has gone, it seems to show that. First, very few medically treated cases have gone five years without recurrence of symptoms (compare with Table V), and, second, in any year after hospitalization, approximately 75 per cent of the cases are free of symptoms, *i.e.*, satisfactory, and 25 per cent are having symptoms (compare with Table VI).

A study of the status of the postoperative patients according to calendar years, instead of postoperative-years, is not tabulated here. It brought out only one fact of interest, namely, that the proportion of individuals free of symptoms from year to year remained nearly constant. We could show no increase in symptoms in the group as a whole during the depression years, although we were impressed in the Follow-Up Clinic by the apparently close relation in certain individuals between increased economic stress and recurrence of ulcer symptoms.

TABLE VI (a)  
RESULTS BY YEARS  
GASTRIC ULCER

Yrs P O	Partial Gastrectomy, Billroth II and Pólya				Excisions Cauterizations, Pyloroplasties				Posterior Gastro- enterostomy			
	Satis Cases		Unsat Cases		Satis Cases		Unsat Cases		Satis Cases		Unsat Cases	
1	28	88%	4	12%	7	70%	3	30%	9	79%	4	21%
2	25	96%	1	4%	9	90%	1	10%	5	50%	5	50%
3	23	96%	1	4%	7	88%	1	12%	2	29%	5	71%
4	22	95%	1	5%	7	88%	1	12%	1	20%	4	80%
5	18	100%	0		5	83%	1	17%	1	25%	3	75%
6	15	100%	0		5	100%	0		1	33%	2	67%
7	14	100%	0		4	80%	1	20%	0		2	100%
8	13	100%	0		3	100%	0		0		2	100%
9	11	100%	0		3	75%	1	25%	0		0	
10	11	100%	0		2	50%	2	50%	0		0	
11	6	86%	1	14%	2	67%	1	33%	0		0	
12	5	83%	1	17%	3	100%	0		0		0	
13	4	80%	1	20%	2	67%	1	33%	0		0	
14	3	75%	1	25%	0		1	100%	0		0	
15	2	67%	1	33%	1	100%	0		0		0	

Table VI (a) shows the "Results by Years" in gastric ulcer, just as Table VI shows them in duodenal ulcer. The points of interest in this table are the excellent record of the partial gastrectomies and the very poor record of the gastro-enterostomies.



TABLE VII  
SUMMARY OF UNSATISFACTORY RESULTS  
DUODENAL AND GASTRIC ULCERS

Type of Operation	Unsatisfactory Cases	Poorly Functioning Gastro-ent	Hemorrhage	Recurrent Ulcer	Marginal Ulcer	Jejunal Ulcer	Total Ulcers	Retention	Spastic Jejunum	Neurosis	Reoperation	Died of Ulcer During Follow-Up
Gastro enterostomy	12	6	6	4	3	2	9	4	0	1	3	1
Obstruction group												
Gastro-enterostomy	19	1	11	2	2	1	5	1	0	1	3	2
Hemorrhage group												
Gastro-enterostomy	50	16	13	10	14	2	26	9	2	3	11	1
Pain group												
Totals	81	23	30	16	19	5	40	14	2	5	17	4
Partial Gastrectomy												
Billroth II and Polya	13	1	4	1	4	2	7	1	0	0	2	1
Duodenal ulcer												
Partial Gastrectomy												
Billroth II and Polya	3	1	1	0	0	1	1	0	0	0	0	0
Gastric ulcer												
Pyloroplasty	8	0	4	3	0	0	3	2	0	0	1	0
Duodenal ulcer												
Pyloroplasty	3	0	2	0	0	1	1	0	0	0	0	0
Gastric ulcer												
Post gastro enter	10	0	5	0	0	0	0	0	0	0	0	3
Gastric ulcer												

In Table VII an attempt is made to analyze the causes of failures occurring after the operations that were performed most frequently. A total of 314 individuals were followed after these operations, of which 118 sooner or later became, temporarily at least, unsatisfactory. This table was arranged in order to show whether any one procedure was especially prone to be followed by any single cause of failure. Pain is not included in this table as it occurred in nearly all these patients, whatever their operation. It does not appear from this record that there is any undesirable result which occurs after one type of operation more than after another. Hemorrhage occurred among the unsuccessful cases after all operations in not very different proportion. It occurred regardless of whether the patient had bled before operation or not. Recurrent, marginal or jejunal ulcers, demonstrated chiefly by roentgenologic evidence, appeared in about half the unsuccessful gastro-enterostomies and half the unsuccessful partial gastrectomies. Poorly functioning stomas appeared relatively more frequently among the gastro-enterostomies. Neuroses, so diagnosed by a psychiatrist, are found in only five cases, but this figure is probably lower than it would be if adequate psychiatric examination were possible for all the patients. Certainly this is a complication that should be recognized, if possible, before operation is undertaken, as few of these individuals are subjects for surgery.

The number of wholly unsuccessful cases, compared with those who had only temporary or mild recurrences, may also be estimated from this table. In the two right-hand columns appear the number of individuals that were subjected to secondary operations because of the severity of their recurrences, and the number that died of their ulcers. Among the 118 patients, there were 20 secondary operations, of which six were partial gastrectomies after unsuccessful gastro-enterostomies, six were closures of gastro-enterostomy stomas, and the remainder were miscellaneous procedures. It is interesting that only two of these operations were for acute perforations. Of the eight deaths, four were attributed to hemorrhage, two occurred after secondary operations, one followed the development of carcinoma at the site of an old gastric ulcer, and one is unclassified.

The question of how often carcinoma develops in previously benign gastric ulcers is not in any way answered by our data. Among a total of 88 gastric ulcers, we have observed three die of gastric carcinoma, but we do not know that these three did not have carcinoma at the time they first developed symptoms. We have included them among the ulcers because none of them was recognized to have carcinoma in less than five years after the recognition of the ulcer. Other cases with carcinoma have been placed with the carcinoma group, whatever the diagnosis made at the time of operation. The point of practical importance in this matter is the recognition of the difficulty of distinguishing between the benign and malignant ulcers in the stomach even at operation. With the good results that have come of partial resections for benign ulcers, we are more encouraged than ever to resect doubtful cases that do not heal rapidly under medical care.

TABLE VIII

## POSTERIOR GASTRO ENTEROSTOMY FOR DUODENAL ULCER

## CHIEF CAUSES OF DEATH

Pneumonia	7
*Hemorrhage	7
Peritonitis	2
Ileus	1
Dilated stomach	1
Pulmonary embolus	1
Miliary tuberculosis	1
During operation	1
Inanition	1
Lung abscess	1
	—
Total	23

Autopsies 13—57%

- \*2 from ulcer bed  
 2 from undetermined source  
 2 from G E suture line  
 1 from abdominal wall

The postoperative death rates shown in Table I and II are higher than most of those which have been published. Table VIII gives the chief causes of death after gastro-enterostomy for duodenal ulcer. Over half of these cases were autopsied. Pneumonia appeared to be the chief cause in approximately one-third of the cases. Hemorrhage was the chief cause in another third. It is to be noted that at least two of the fatal hemorrhages occurred from the ulcer bed. Whether these two would have occurred without operation is impossible to tell. But this table affords a poor explanation of why so many died.

TABLE VIII (a)

## POSTERIOR GASTRO-ENTEROSTOMY FOR DUODENAL ULCER

## MORTALITY ACCORDING TO AGE

Age Years	No of Cases	P O Deaths	Death Rate
11-20	7	0	0
21-30	31	0	
31-40	73	6	7.1%
41-50	54	3	
51-60	44	9	23.3%
61-70	15	4	
71-80	1	1	
	—	—	—
	225	23	10.2%

Table VIII (a) is perhaps more significant, showing how the mortality rate rose with the age of the patients operated upon. Under 30, there were no deaths, between 30 and 50, there were nine deaths among 127 patients (7.1 per cent), but in patients over 50 the death rate was 23.3 per cent. Another factor, that we cannot appraise accurately, is the condition of the patients before operation, irrespective of age. About one-third of those that died were in poor condition before operation, due to hemorrhages, too prolonged medical regimen without improvement, or other causes. In the earlier years of this study, prolonged dehydration before operation was not uncommon. It is clear from these considerations that the operative risk in gastro-enterostomy cannot be stated for any individual in terms of the average, as is true in most operations.

TABLE VIII (b)  
POSTERIOR GASTRO-ENTEROSTOMY FOR DUODENAL ULCER  
MORTALITY BY FIVE-YEAR PERIODS

Years	Total No of Cases	Postop Deaths	Survivors
1916-1920	32	4 12.5%	28 87.5%
1921-1925	60	9 15%	51 85%
1926-1930	60	5 8.3%	55 91.7%
1931-1935	70	5 7.1%	65 92.9%

Table VIII (b) shows that the postoperative mortality of gastro-enterostomy has fallen during the last decade to about half of what it was during the previous decade. So many factors seem to have contributed to this drop that we have not attempted to analyze them.

The mortality rate in partial gastrectomies has been even more of a problem than in gastro-enterostomies. In all types of partial gastrectomy, there were 22 deaths in 133 cases, a mortality rate of 16.5 per cent. In duodenal ulcers the rate was 18.5 per cent, in gastric ulcers 13 per cent. Table IX gives an analysis of the chief causes of death in the two types of partial gastrectomy most often performed, namely, the Billroth II and Pólya types. It is not easy even at autopsy to assign a chief cause of death in several of these cases. They died with multiple lesions. But Table IX is wholly clear as to the importance of one item, namely, peritonitis from leakage of the duodenal stump. At least six of the 16 fatalities were traceable to this cause, and there is little doubt that some of the three labeled "Uncertain" and the two labeled "Peritonitis of Unknown Source" could be added to this number. So that somewhere between 37.5 and 68.8 per cent of our deaths are attributable to leakage! Of perhaps even greater importance is the item of obstruction, which we know occurred in nine of the 16 fatalities and may have been present in five more. By obstruction we refer to kinks or twists occurring close to the site of anastomosis in either the proximal or distal jejunal loops.

Four of the six proven leaking duodenal stumps were associated with, and probably partly caused by, such obstructions. A reduction of mortality must obviously await control of these two complications.

TABLE IX

## PARTIAL GASTRECTOMY FOR DUODENAL AND GASTRIC ULCER

		P O	Deaths	Autopsies
Billroth II	54	8	14 8%	2
Pólya type	55	8	14 8%	7
Totals	109	16		9

## CHIEF CAUSES OF DEATH

	Bill II	Pólya	Total
Uncertain	3	0	3
Peritonitis, unknown source	2	0	2
Hemorrhage	1	1	2
Leakage of duodenal stump	2*	4†	6
Obstruction alone	0	3	3
Totals	8	8	16

\* 1 also had obstruction

† 3 also had obstruction

TABLE IX (a)

## PARTIAL GASTRECTOMY

*Complications, Not Fatal, but Requiring Second Operation*

	Bill II	Pólya	Total
Peritonitis, unknown source	1		1
Atonic stomach	1		1
Leakage of duodenal stump	0	2	2
Obstruction alone	0	5*	5*
Totals	2	7	9

\* One of these after 16 months

TABLE IX (b)

## PARTIAL GASTRECTOMY

*Serious Complications*

Atonic stomach	1
Hemorrhage	2
Peritonitis, unknown source	3
Uncertain nature	3
Leakage of duodenal stump (of which 4 had obstruction also)	8
Obstruction alone	8
Total	25

In addition to the complications which ended in death, there were, in other individuals, complications which required operative interference to save life early during the postoperative course. These are listed in Table IX (a), and here again appear leakage of the duodenal stump in two of the nine cases, and obstruction in five. (One of these obstructions was evident shortly after operation but was incomplete and did not necessitate immediate relief.) A summary of the serious complications, some of which resulted in death, is given in Table IX (b), combining the figures in the two preceding tables. For emphasis, attention is again drawn to the frequency of leaking duodenal stumps and obstruction.

The question immediately comes to mind: How to control these two complications? For the leaking duodenal stump, a drain placed near to the site of the stump, almost as a routine measure, should usually suffice. Not one of the surgeons who operated upon the eight cases that leaked thought that his closure of the stump was insecure, or he would have drained. One cannot predict which of the stumps will yield to the pressure caused by unexpected obstruction, even temporary, or to some other circumstance. Therefore we drain. In several cases where the closure was recognized to be faulty, a drain was employed. Some of these cases developed fistulae, but not one has died. The fistulae, incidentally, have all closed spontaneously, as would be expected provided there were no obstruction to the flow of duodenal contents down the intestine.

As regards the second complication, obstruction, no such simple remedy suggests itself. The obstructions have occurred in either the proximal or distal anastomosing loop of intestine. They have occurred from twists, kinks or constrictions and as the result of edema. Some were brought about by adhesions, some by constriction by the transverse mesocolon when it happened to slip down from the stomach and encircle the anastomosed jejunal loop. It is true that obstructions appear to have occurred much more frequently after the Pólya type of operation than after the Billroth II type (Table X).

TABLE X  
POSTOPERATIVE OBSTRUCTION

Proximal Loop	
Anterior Pólya (without entero-enterostomy)	3
Posterior Pólya (without entero-enterostomy)	1
Posterior Pólya (with entero-enterostomy)	2
Billroth II	0
Distal Loop	
Anterior Pólya (without entero-enterostomy)	2
Posterior Pólya (without entero-enterostomy)	1
Posterior Pólya (with entero-enterostomy)	2
Billroth II	1
At Site of Anastomosis	
Billroth I	1

It would seem from analyzing the statistics in Table X, that the answer was to abandon Polya and adopt the Billroth II, since the follow-up results were almost equally good. But it is to be recalled that the death rates in the two operations were the same. Seven of the eight deaths after Polya were followed by autopsy, but only two of the eight deaths after Billroth II. Therefore, we do not know that the Billroth II operation leads as infrequently to obstruction as we think it does, and see little in our results to make us recommend it over the Polya.

TABLE XI  
PARTIAL GASTRECTOMY FOR PEPTIC ULCER

Operation	Total No of Cases	Mor- tality	Fol- lowed Sur- vivors	Followed Sur- vivors		Postoperative Complications			
				Satis- factory		Obstruc- tion		Peri- tonitis	
Billroth II	54	8 15%	41	32 78%		1 2%		5 9%	
Polya	55	8 15%	45	38 84%		11 20%		6 11%	
a Ant Polya	26	4 15%	21	16 77%		5 20%		4 15%	
b Post Polya	29	4 15%	24	22 92%		6 21%		2 7%	
c Polya with ent-ent	19	4 21%	14	12 86%		4 21%		3 16%	
d Polya without ent-ent	36	4 11%	31	26 84%		7 19%		3 8%	
Billroth I	7	1 14%	6	4 67%		1 14%		0 0	
Moynihan	4	2 50%	2	0 0		0 0		1 25%	
Sleeve	13	3 23%	10	4 40%		0 0		1 8%	

#### In Gastric Ulcers

Of 16 Polyas followed, 15 were satisfactory

Of 15 Billroth II followed, 13 were satisfactory

Of 31 Polyas and Billroth II followed, 28 were satisfactory, or 90.3%

#### In Duodenal Ulcers

Of 29 Polyas followed, 23 were satisfactory

Of 26 Billroth II followed, 19 were satisfactory

Of 55 Polyas and Billroth II followed, 42 were satisfactory, or 76.4%

The final part of this study deals with three matters. First, a comparison of the results after anterior Polya as compared to posterior Polya, second, of Polya with entero-enterostomy as compared to Polya without entero-enterostomy, and third, the results after Polya and Billroth II procedures compared with the results after the other types of partial gastrectomy which have been performed. On analyzing the statistics in Table XI, it is seen that there is little to choose between anterior and posterior Polya from the standpoint of postoperative mortality, follow-up results, or incidence of postoperative complications. The same is true in comparing the Polya with entero-enterostomy to those without entero-enterostomy. The posterior Polya has been followed by more satisfactory survivors, proportionately, than has the anterior Polya, but this difference is explained by the fact that posterior pro-

cedures happened to be done more frequently in the gastric ulcers, in which the results were good whichever of the two procedures was performed. It is interesting that the presence of an entero-enterostomy does not appear to lower the incidence of postoperative obstruction.

With regard to the partial gastrectomies other than Pólya or Billroth II types, the column showing "Followed Survivors Satisfactory" in Table XI explains why the Billroth I, Moynihan and sleeve resection types of procedures are now rarely performed. Few, in our experience, have been followed by satisfactory results. The postoperative death rate after the Moynihan and sleeve resections has been high. It is true, however, that we have performed the Moynihan operation only four times.

Of pyloroplasty, in our experience, not much is to be said. The series is small, 27 in all, of which three were performed for gastric ulcer and the remainder for duodenal ulcer. What little difference can be demonstrated between the Finney and Horsley types is in favor of the former. Tables I and II show the results in the duodenal ulcers. They are encouraging when compared to the results of other procedures, especially as regards the low death rate, but the follow-up is not yet long enough to judge. In the Horsley type, followed for an average of 4.6 years, five out of 11 cases are already unsatisfactory. Only two of the Finney type have remained satisfactory for more than two years, although five others are still free of symptoms, followed for less than two years. The percentage of time free of symptoms after both operations has been good and there has been no death from ulcer after leaving the hospital. None of the other procedures, comprising the smaller groups, holds promise.

### CONCLUSIONS

(1) Cases of peptic ulcer should be given the benefit of the safest known treatment first, namely, medical or conservative therapy.

Its definite limitations in certain resistant cases, however, or in the presence of repeated or persistent serious complications, should be recognized. Obstruction, uncontrolled erosion, with or without perforations and hemorrhage, are among the most formidable of these. Cancer in gastric ulcer must always be borne in mind.

A careful study of each patient before operation is the most valuable guide in selecting the proper surgical procedure. This statement does not minimize the importance of the findings at operation.

(2) Despite the present radical trend in surgery, there is a very definite field for gastro-enterostomy in the treatment of this disease, in fact, in cases with persistent obstruction of high grade, it is followed by as satisfactory results as is any other form of surgery. It presents less risk to the patient than more radical procedures.

(3) Subtotal gastrectomy is indicated in pyloric or duodenal ulcer in which persistent pain or recurrent hemorrhage is outstanding. Gastro-enterostomy in these cases has proven unsatisfactory.



(4) Cases of chronic gastric ulcers of the lesser curvature with persistent symptoms of a serious nature respond best to subtotal gastrectomy

(5) Subtotal gastrectomy is a more formidable procedure than gastro-enterostomy and, therefore, will be associated inevitably with a higher post-operative mortality. Its present operative mortality can be lowered by a fuller realization of the actual causes of death

(6) The material is not available in this clinic for a reasonable study of the results of the various forms of pyloroplasty

(7) It is obvious that study of peptic ulcer should be directed toward etiology, but until the cause is known, effort should be directed not toward more radical surgery, as is the present trend, but rather toward selective surgery. This selection can be made best only if follow-up results are known

As surgeons, it is our responsibility to select the patient for operation and the operation for the patient

# CARCINOMA OF THE PERIPAPILLARY PORTION OF THE DUODENUM

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## PART ONE

THIS is our third communication dealing with the subject of duodenal carcinoma, the two previous papers being devoted to a consideration of this lesion as it occurs in the suprapapillary portion (Stewart and Lieber) and infrapapillary portion (Lieber, Stewart and Lund) of this short segment of the small intestine. An analysis of carcinoma of the peripapillary portion of the duodenum appears justified in view of the fact that a comprehensive picture of the morbid anatomic and clinical aspects of the disease is lacking, and only slight notice has been given to it in current clinical, surgical and neoplastic treatises.

The papilla of Vater is a small but complex structure with variable anatomic relationships. It is covered superficially with intestinal mucous membrane and it receives the common bile duct and main pancreatic duct, which occasionally unite to form a true ampulla within the papilla proper. We shall cite from our own material and from the literature to show that cancer can arise from the epithelial lining of any of these structures. These tumors, however, early permeate the surrounding tissues and by extension soon involve adjacent structures and so obscure the exact point of origin of the neoplasm. Under these circumstances, which obtained in the majority of cases, there is no way of identifying exactly the structure giving rise to the growth. It is then only possible to classify each case on the basis of the extent of involvement at the time of examination either at operation or autopsy. We incline to the belief, at least with regard to certain of our own cases, that, had the postmortem examination been more painstaking, the gross exploration carried out more diligently, and the tissue blocks for microscopic study selected more judiciously, a greater refinement of classification would be possible. Moreover, the terms ampulla of Vater and papilla of Vater are frequently used interchangeably in many protocols, as though they were synonymous words capable of indicating the same anatomic structure.

The cases of carcinoma of the peripapillary portion of the duodenum in this series may be classified as follows (I) Primary carcinoma of the ampulla of Vater (II) Primary carcinoma of the terminal duct of Wirsung (III) Primary carcinoma of the terminal common bile duct (IV) Primary carcinoma of the intestinal mucous membrane covering the papilla of Vater (V) Carcinoma involving all the epithelial structures of the papilla of Vater under Groups I, II, III and IV (VI) Carcinoma involving all the epithelial structures comprising the papilla of Vater exclusive of the intestinal mucous membrane

We propose to present here an analysis of certain features of carcinoma of the peripapillary region of the duodenum and to report 17 new cases of this condition. An attempt was made to collect all the cases reported in the literature, but a few were not available and others undoubtedly escaped our notice, especially where reported in monographs, old systems, obscure journals or under misleading titles. Since many histories were incomplete, inaccuracies and omissions existed in other data, and standards of observation and interpretation were lacking, the numerical sum of the analyses of given clinical or pathologic features does not always equal the total number of cases under consideration.

Three hundred ninety-nine cases were abstracted from the literature. There are included in this study, however, only those cases which have a history, physical findings and gross and microscopic studies of the primary lesion. On this basis, 205 were analyzed, to which are added the 17 cases from our own records. Thirty cases, usually having been regarded as examples of this condition, were rejected from present consideration because of the brevity of the report or lack of history or physical examination. Six cases were discarded because of the possibility that the neoplasm may have been primary in the stomach in two cases, in the gallbladder and kidney in one each, while in one case the neoplasm was not definitely malignant, and in another, the tumor was probably a malignant melanoma. One hundred fifty-eight cases were rejected because of the lack of gross and microscopic studies of the primary lesion.

Appended are lists of the sources of the case reports of those cases judged acceptable for analysis (222), and those which were rejected for the reasons given (194).

#### CITATION OF THE SOURCE OF THE 222 CASES ANALYZED

Fereol, Rosenstein, Merkel, Cases 1 and 2, Caillet, Bridge, Fischel, Berry and Cockle, Barth and Marfan, Sacci and Aderson, Ely, Moran, Pilliet, Coats and Finlayson, Warmburg, May, Koster, Schmitt, Cases 1 and 2, Weir, Hesper, Case 1, Holbuer, Case 2, Ely, Lannois and Courmont, Deetjen, Rendu, Hanot, Hanot, Thomas and Noica, Mauclair and Durrieu, Krokiewicz, Hughes, Descos and Beriel, Dominici, Dieckmann, Luzzatto, Dobbertin, Butz, Rolleston, Schuller, Cases 1 and 2, Mayo, Edes, Rinford, Maury, Scheuer, Miodowski, Cases 1 and 4, Hall, Hagen, Cornil and Chevassu, Moore, Klotz, Cases 1 and 2, Hultgren, Letulle and Verliac, Chardon and Raviart, Arnsperger, Cases 28 and 30, Raviart and Lorthois, Carnot and Harvier, Geiser, Case 2, Pappenheimer, Verhoogen, Souques and Aynaud, Cases

1 and 2, di Giovine, Le Blanc, Borehus, Case 4, Devic and Savy, Gasbarini, Rauzier, Rimbaud and Anglada, Le Noir and Courcoux, Korte, Case 32, Koerber, Cases 1 and 2, Oehler, Navarro, François-Dainville, Doberauer, Cuneo, Kausch, Cases 1, 2 and 4, Lenormont and Courmont, Cade, Oppenheimer, Upcott, Case 2, Roger and Lapeyre, Outerbridge, Binda, Pollet, Zuccola, Cases 1, 2, 3 and 4, Docq and Van Bever, Crohn, Cases 1, 2 and 3, Petren, Case 56, Anschutz, Oliani, Case 9, Schussler, Case 9, Ristori, McGuire and Cornish, Case 1, Pallin, Cases 1, 2 and 3, Carnot and Libert, Propping, Lewis, Brutt, Cases 6 and 7, Kleinschmidt, Cases 1 and 2, Tenani, Hartmann, Angeli, Pozzi, Cases 2 and 3, Prat, Case 1, Marino, Abell, Cases 2 and 3, Chiray, Benda and Milochevitch, Einhorn and Stetten, Pozzi, Cases 1 and 2, Konjetzny, Muller, Hadfield, Cabot, Case 12063, Garcia Lagos, Ugon and Domuniquiez, Hingst, Cases 1, 2 and 3, Clar, Fulde, Rouslacroix, Raybaud and Debernardy, Cohen and Colp, Cases 1, 2, 4, 5 and 8, Murgoci, Case 1, Savynych, Cases 1 and 2, Del Valle, Brachetto-Brian and Orosco, Case 2, Busch, Dewis and Morse, Case 6, Boston and Jodzis, Jermain, Bonanno, Countryman, Meyer and Rosenberg, Case 1, Sisto, Varangot, Cases 1 and 14, Ross and Davie, Godfrey and Sappington, Mateer and Hartman, Cases 2, 3, 4 and 5, Rutishauser, Cases 2, 3 and 6, Walters, Pemberton, Judd, Block, Goldberg, Potter, Berard, Mallet-Guy and Croizat, Lauwers, Cases 1 and 2, Cabot, Case 19191, Lisa, Levine and Fitz Hugh, Lami, Santero, Cases 1 and 2, Swenson and Levin, Chiuchini, Harbin, Harbin and Harbin, Whipple, Parsons and Mullins, Cases 1, 2 and 3, Hunt and Budd, Doub and Jones, Case 2, Koch, Case 2, Dardinski, Cabot, Case 23282, Geisthovel, Cases I-1, II-1 and II-8, Hoffman and Pack, Cases 3, 8, 11, 12, 15, 16 and 18, La Manna, Case 1 and Lieber, Stewart and Morgan, 17 cases

#### CITATION OF THE SOURCE OF 30 CASES REJECTED BECAUSE OF INSUFFICIENT DATA

Oestreich, Leith, Cases 1 and 2, Lejonne and Milanoff, Krause, Geiser, Case 4, Saltykow, Cases 1 and 3, Schussler, Case 3, Mariconda, Dalla Valle, Cases 1 and 2, Staemmler, Cases 1, 4 and 5, Mosto, Case 2, Plenge, Case 1, Llambias, Brachetto-Brian and Orosco, Case 3, Shapiro and Lifvendahl, Cases 4, 6, 8 and 11, Molfino, Schonbauer and Bsteh, Cases 1, 2, 3 and 4, La Manna, Case 153/31, and Nickerson and Williams, Cases A-35-11 and A-35-217

#### CITATION OF THE SOURCE OF SIX CASES REJECTED BECAUSE OF PROBABILITY OF INCORRECT DIAGNOSIS

Reynolds, Krielke, Zuccola, Case 5, Hoffman and Pack, Case 4, Wahl and Zuccola, Case 7

#### CITATION OF THE SOURCE OF 158 CASES REJECTED BECAUSE OF OMISSION OF PATHOLOGIC EXAMINATION

McNeal, Ehrmann, Stokes, Dittrich, Cases 1 and 2, Lacaze, Duchek, Lambl, Frerichs, Arrachard, Riesenfeld, Case 69, Avezou, Chouppe, Hicks, Martha, Mason, Courmont and Lannois, Frankel, Holtbuer, Case 1, Terrier, Case 1, Thomas, Stabel, Morini, Auerbach, Cases 6 and 7, Kehr, Eilers and Lucke, Case 13, Pratt and Fulton, Halsted, Case 2, Pennato, Cases 1 and 2, Brill, Peaudeleu, Sears, Friedheim, Case 4, Czerny-Arnsperger, Arnsperger, Cases 27 and 29, Cordua, Geiser, Case 3, Boxwell, Aronson, Orth, Lennander, Koster, Chauffard, Bauer, Leclerc, Tartanson and Bonnamour, Stieda, Cases 10 and 13, Cade and Leriche, Morian, Cases 2 and 3, Ollive and Collet, Richards, Barjou and Gate, Paus, Cases 210 and 211, Kausch, Case 3, Upcott, Case 1, Slajmer, Erdmann, Clermont, Zuccola, Case 6, Hirschel, Wrede, Erdmann and Heyd, Case 3, Pels-Leusden, Lichty, Cases 4 and 5, Schussler, Cases 6, 7, 8 and 10, Oliani, Cases 1, 2, 3, 4, 5, 6, 7 and 8, McGuire and Cornish, Case 2, Di Poggio, Gandusio, Blad, Disque, Brutt, Cases 1, 2, 3, 4 and 5, Mucharnski, Pozzi, Case 1,

Dalla Valle, Cases 3, 4, 5, 6, 7, 8 and 9, Vcdel, Giraud and Puech, Abell, Case 1, Staemmler, Cases 6, 7 and 8, Abramowa, Cases 1, 2 and 3, Eusterman, Berkman and Swan, Cases 7, 8, 9, 10, 11 and 12, Gohrbrandt, Joffe, Cases 1 and 2, Cccom, Cohen and Colp, Cases 3, 6 and 7, Dcwis and Morse, Case A, Cabot, Case 15241, Kulakov, Dencks, Cases 3 and 5, Klinkert, Blomstrom, Case 3, Colella, Ramlau-Hanson, Cases 5, 7, 8 and 9, Hinton, Case 2, Varangot, Case 2, Hartmann, Cases 11, 12 and 13, Walzel, Raiford, Cases G-1196, G-9310 and G-9923, Lee and Totten, Case 2, Startz, v Hrabovsky, Case 1, Pangaro, Case 2, Hoffman and Pack, Case 17, and Geisthovel, Cases II-2, 3, 4, 5, 6, 7, 9, 10, 11 and 12

The minutiae of the clinical phenomena evidenced and laboratory data obtained in each of the appended 17 case reports have, to a large extent, been omitted owing to the resultant unessential lengthening of the report, emphasis, however, has been made in detailing the postmortem findings and the results of the pathologic examinations

### CASE REPORTS

**Case 1**—D K, white, male, age 57, was admitted to the Unontown Hospital, December 17, 1935, complaining of pain in the upper abdomen, jaundice, loss of 25 pounds in weight (113 Kg) and vertigo. For the past 40 years the patient had suffered from digestive disturbances after eating certain foods. Such an episode occurred one month before admission to the hospital, followed one week later by jaundice which deepened progressively over a period of two weeks and then diminished somewhat. The appetite remained good, the bowels regular and the stools were clay-colored and foul. Shortly before admission, the patient experienced a dull, aching sensation in the lower abdomen and pain in the epigastrium accentuated by certain foods such as meats, fruits and nuts.

*Physical Examination*—The abdomen was soft and no masses were palpable. There was, however, tenderness over the region of the gallbladder. Roentgenologic studies showed no evidence of gastric malignancy. Icterus index, 80, the bromsulphalein test for liver function showed 70 per cent retention of the dye in 30 minutes (2 mg dosage), the van den Bergh test was immediate direct. *Clinical Diagnosis* Carcinoma of the head of the pancreas. A cholecystogastrostomy was performed 11 days after admission. The convalescence was unsatisfactory, the jaundice increasing appreciably, and death occurred January 2, 1936.

*Autopsy*—Three hours after death Dr H Lund. The combined gross and microscopic diagnoses were (1) Primary adenocarcinoma of the duodenal papilla, (2) obstruction of the common bile and pancreatic ducts, (3) surgical cholecystogastrostomy opening, with extensive hemorrhage into the gallbladder occluding the stoma, (4) jaundice, (5) acute degeneration of liver and kidneys, (6) moderate arteriosclerosis of aorta, (7) marked myocardial degeneration, (8) congestion and edema of lungs, (9) biliary stasis of liver, (10) chronic pancreatitis, (11) biliary nephrosis, (12) bilateral adenoma of adrenal glands, and (13) absence of right testicle.

There was slight edema of the extremities. The margins of the abdominal incision were well approximated superficially, but in and beneath the muscle layers there was a moderate amount of extravasated blood. Near the upper pole of the incision there was a small hematoma which communicated with the peritoneal cavity through a small gap in the serosa. The peritoneal cavity contained 600 cc of red, watery fluid and there were large clots of blood about the gallbladder. The serosa was everywhere smooth and glistening.

All the cardiac chambers and valvular rings were dilated, the endocardium was stained yellow and the myocardium was soft. The lungs were voluminous, heavy, con-

gested and edematous in the dependent portions. The kidneys were deep green and the markings on the cut surface were indistinct.

The esophagus showed nothing noteworthy. The stomach was dilated to a capacity of 2,000 cc and its wall was thin and attenuated. On the anterior superior aspect, 4 cm proximal to the pylorus, there was an opening 1.5 cm in diameter. This communicated with the cavity of the gallbladder which was distended with firm blood clots. Bile could not be forced through this cholecystogastrostomy opening.

Upon opening the duodenum, the papilla of Vater was located 7 cm from the pyloric ring and appeared as a cylinder, 1.5 cm long and 1.3 cm in diameter, projecting outward and downward from the wall of the duodenum. It was moderately firm and its sides were apparently covered by duodenal mucous membrane. Its distal end was slightly rounded and presented a finely lobulated surface. On incising through the mass into the common bile duct, a moderate amount of mucoid fluid escaped. The ampulla of Vater felt slightly nodular, principally on its inferior and right surfaces,

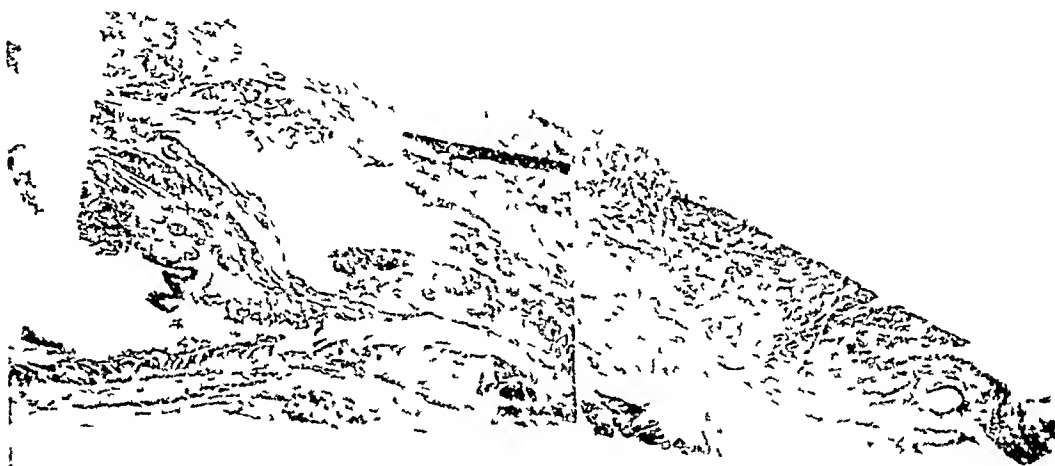


FIG 1—Case 1. A triangular section through the ampulla of Vater. The base is formed by portions of the muscular wall of the duodenum and pancreas. The hypotenuse is formed by the wall of the common bile duct. The upright side is formed, in its lower portion, by the reflected mucosa of the duodenum and the upper portion by the projecting papilla of Vater. ( $\times 7$ )

and the mucous membrane was light yellow and glistening. The wall of the ampulla was thickened by moderately firm, homogeneous light yellow tissue which was most abundant near the junction with the duodenum. Higher up, around the bile duct, this tissue faded into light gray streaks resembling fibrous tissue which was continuous with similar tissue in the pancreas. The common bile duct measured 2 cm and the common hepatic duct 2.7 cm in circumference.

The liver weighed 1,400 Gm. It was greenish-yellow, softer than normal, and the cut surface showed dilated biliary ducts.

The pancreas measured 18 cm in length and was tough, with indistinct lobules. In the body of the organ the pancreatic duct measured 2.3 cm in circumference and in the tail, 1.8 cm. It narrowed considerably toward its termination, coursing parallel with the common duct, and emptied into the duodenum through the ampulla of Vater just behind the orifice of the common duct. The pancreatic tissue was extensively atrophied, especially in the body of the organ, where it formed a grayish-yellow tough wall 6 mm thick around the pancreatic duct. The head of the pancreas was very hard, cut with increased resistance and on section appeared to be mainly made up of tough grayish-yellow fibrous tissue containing a few small yellow areas which were taken to be pancreatic lobules. No enlarged lymph nodes were observed. The small intestines were moderately dilated and filled with gas and mucus.

*Pathologic Examination*\*—A roughly triangular section of the ampulla of Vater was obtained for histologic examination, after the common duct was opened. A portion of the wall of the duodenum was attached to one corner of the section corresponding to the right angle (Fig 1). The mucosa of the duodenum was reflected upward on the upright side while the muscular layer formed part of the base of the triangle. The greater portion of the upright side of the triangle (1.75 cm) was formed by the projecting papilla of Vater, the hypotenuse (4 cm) was formed by the wall of the common bile duct, the base (3.8 cm) was composed of portions of the muscular wall of the duodenum, and pancreas. The papilla of Vater overhung the duodenum a little where the two structures met. A deep cleft traversed the section from the middle of the vertical side to the middle of the base, paralleling the hypotenuse or common duct. This structure will be referred to as "pancreatic duct." It was either the duct of Wirsung or a deep cleft between two very long villous-like projections. It appeared to terminate between the lobules of the pancreas. Its epithelium on the surface was autolyzed in places, but otherwise its structure was no different from the remainder of the atypical epithelium.

This "pancreatic duct" ended abruptly about 2 cm from the tip of the ampulla, terminating in a pocket lined by flattened cells, surrounded by fibrous tissue and lying between atrophic pancreatic lobules. The strip of duodenal mucosa showed autolytic changes in the superficial epithelial cells but the outlines of the cryptic villi and Brunner's glands remained. Where the duodenal mucosa was reflected onto the papilla of Vater it narrowed abruptly and was capped by masses of atypical epithelial cells, and the underlying duodenal musculature faded out into the walls of the common duct and "pancreatic duct." These atypical epithelial cells lined both ducts and permeated extensively the deeper strands of fibrous and muscular tissue almost throughout the limits of the section, that is, about 3.5 cm from the tip of the ampulla. Approximately 1 cm of the distal end of the common duct was lined by nonmalignant partially autolyzed epithelium. The atypical epithelial cells measured approximately 10 micra in width and 50 micra in length and were characteristically arranged in a single layer, with the nuclei occupying the basal fourth of the cell. With this essential structure predominating, the epithelium was occasionally differently arranged to afford a small variety of appearances. On the surface there were numerous villous-like projections supporting numerous secondary papillary projections arranged in a parallel fashion, resembling duodenal crypts, although much wider. In the deeper tissues these large villi were less evident, and acinar structures predominated which were lined by single-layered epithelium either indented by papillary projections or traversed by fibrous septae.

The most common picture in the deeper tissue was that of large acini, almost completely filled with desquamated epithelium and imperfectly lined by single layers of epithelial cells. The individual cells were tall columnar with light pink, slightly foamy cytoplasm and sharply defined cell borders. The nuclei were generally ovoid or round and composed of a delicate stippling of chromatin material. Some cells had large hyperchromatic nuclei with coarse masses of chromatin. About one mitotic figure was observed in every two or three high power fields. The stroma was composed of fibroblasts, capillaries and inflammatory cells and formed broad bands on the surface supporting the villous-like projections. Several strands of smooth muscle were observed in the depth of the section and these were infiltrated by tumor cells. However, the large strip of duodenal musculature and underlying pancreas did not seem to be invaded.

A section of pancreas was obtained from the head of the organ close to the common duct. The major part of the section was composed of mature, occasionally hyalinized fibrous tissue in which there were small ducts, atrophied lobules and islet tissue. The

\*The pathologic examinations in all of the 17 cases reported herewith were made by Drs. Marshall M. Lieber and Harold L. Stewart.

intralobular and periductal fibrous tissue was increased and infiltrated with chronic inflammatory cells

The inner half of the liver lobule was sharply demarcated owing to the anuclear, deeply pigmented and granular state of the hepatic cells. The pigment varied somewhat in amount in individual hepatic cells but in general was abundant, appearing as a fine stippling of large green granules, and bile thrombi were numerous in the canaliculi. In the peripheral zone the nuclei were generally well preserved and the cytoplasm contained relatively much less pigment. Some cells were multinucleated and the nuclei varied in size, some being hyperchromatic. The portal radicals were moderately thickened by fibrous tissue and infiltrated with small round cells and occasionally neutrophils.

The most striking change in the kidneys involved the convoluted tubules and consisted of extensive degeneration, necrosis and pigmentation. In the collecting tubules fewer of the cells were necrotic but many were swollen and granular and a few contained pigment. Bile pigment in the form of granules and casts was present in the lumens of the tubules. A few wedge-shaped or linear streaks of atrophic renal tissue were observed near the surface.

**Case 2**—M. M., a white female, age 58, was admitted to the Philadelphia General Hospital, July 23, 1934. She had become acutely ill one month previously with nausea and epigastric pain but was unable to vomit. The pain was dull in character and localized under the right ribs. Jaundice appeared two weeks later and the urine became dark brown and the stools gray-colored.

*Physical Examination* of the abdomen was unsatisfactory owing to the marked obesity (220 pounds [100 Kg]), it was, however, distended. Enlargement of the liver was present but no tenderness or palpable masses were noted. Roentgenographic examination of the gallbladder showed failure of the viscus to concentrate. The icterus index varied from 116 to 135 and the van den Bergh reaction was immediate positive. The patient gradually became weaker and died in coma, August 28, 1934.

*Autopsy*—Seven hours after death Dr. R. A. Mathews. The combined gross and microscopic diagnoses were: (1) Adenocarcinoma, primary in the region of the papilla of Vater with extension to the pancreas and metastasis to the lung, (2) hydrohepatosis with marked jaundice and marked degeneration of the liver, (3) obstruction of pancreatic ducts, chronic pancreatitis and foci of fat necrosis, (4) bile pigmentation of kidney and marked nephrosis, (5) arteriosclerosis of aorta and coronary arteries, (6) myocardial degeneration and sclerosis of mitral and aortic valves, (7) generalized passive congestion, and (8) bronchopneumonia.

The gastro-intestinal mucosa appeared congested and the contents of the colon were clay-colored. At the papilla of Vater there was a small, dense, firm, yellow nodule 1 cm in diameter. By compressing the gallbladder with considerable force, bile could be forced through the opening of the papilla into the duodenum. Proximal to the obstruction the biliary passages were markedly dilated. The gallbladder was distended downward 4 cm below the costal margin, its wall was thick, the mucous membrane smooth and bile-stained and it contained thick black-brown bile. The liver weighed 2,020 Gm, its capsule was smooth and the parenchyma was yellowish-brown and friable with small, indistinct lobular markings. The pancreas was enlarged and the cut surface showed patches of yellow necrotic material and a pitted, honey-combed appearance due to dilated ducts.

*Pathologic Examination*—A section was taken through the duodenum including all coats and a small amount of fat and connective tissue externally. No evidence of the papilla, bile ducts or pancreatic duct was observed in this section. The mucous membrane and underlying glands of Brunner appeared intact. Tumor tissue was observed in the submucous and muscular coats and the fibro-fatty tissue outside the duodenum. Tumor cells were observed in and around blood vessels and nerves. The atypical cells grew in the form of small irregular acini and clumps. They were chiefly



columnar or cuboidal and were relatively small with smooth, pale or bright red cytoplasm and small oval nuclei which were exceedingly hyperchromatic although regular in shape. A few of the tumor cells were large, irregular and multinucleated, mitotic figures were rare. The stroma was abundant and consisted of dense, hyalinized fibrous tissue, comparatively avascular and containing only a few inflammatory cells. Large areas were completely necrotic and in these there were small hemorrhages.

FIG 2



FIG 3

FIGS 2 and 3—Case 2. Two views of a large duct embedded in pancreatic tissue. The lumen of the duct is slit-like and there are several shallow areas of ulceration on the surface. The mucous membrane is permeated with densely packed neoplastic tissue. ( $\times 10$  and  $\times 40$  respectively)

Another section passed through a large duct, 0.4 cm in diameter and with a narrow slit-like lumen embedded in pancreatic tissue (Fig 2). The mucous surface of this duct, its entire wall and the surrounding tissue were composed of densely packed neoplastic tissue resembling that just described (Fig 3) and there were several shallow areas of ulceration on the surface.

Sections of the pancreas showed dilatation of ducts, atrophy, fatty infiltration, extensive fibrosis, large areas of necrosis involving pancreatic and fat tissue with associated inflammatory cell reaction including lymphocytes, polymorphonuclear leukocytes and mononuclear cells. The islands of Langerhans tended to persist in the areas of atrophy and fibrosis.

The myocardium showed fibrosis, fatty infiltration and acute degeneration. A section of lung contained a single small metastatic nodule. There were areas of bronchopneumonia and thrombosis of the pulmonary vessels. The adrenal gland contained many focal collections of lymphocytes, especially in relation to the veins. The kidney showed a moderate grade of biliary pigmentation, and marked degeneration and necrosis of tubular epithelium. There was widespread necrosis and disintegration of the liver tissue, less than 5 per cent of the hepatic cells appearing viable. Many of the hepatic cells were vacuolated and there was marked biliary pigmentation. The portal areas were thick and fibrous, and contained many lymphocytes and small proliferating bile ducts.

**Case 3**—T. I., white, male, age 48, was admitted to the Philadelphia General Hospital, February 1, 1934, complaining of epigastric pain and exhibiting deep jaundice. He had had painful attacks accompanied by jaundice in 1929, and again in 1932. *Clinical Diagnosis* Acute cholecystitis. Cholecystectomy was performed, August 29, 1932, at another hospital. With persistence of the symptoms, the patient was again operated upon December 19, 1932, a duodenostomy and removal of a fistulous tract being performed. The terminal illness developed January 20, 1934, characterized by a steadily deepening jaundice and clay-colored stools followed ten days later by sudden sharp pain in the right upper quadrant of the abdomen. There had been no nausea or vomiting at any time.

*Physical Examination* demonstrated a rounded abdomen, somewhat distended and extremely tender and rigid over the epigastric area, there were no masses, however, and the liver was not palpable. Roentgenographic studies of the gastro-intestinal tract showed the stomach in the midabdomen, hypotonic and slightly ptosed with the greater curvature below the iliac crest. Peristaltic movements were inactive and passed uninterruptedly along both curvatures. The duodenal cap was visualized and seemed normal. About 20 per cent of the barium was retained at the end of six hours. *Roentgenologic Diagnosis* Duodenal adhesions and enlargement of the liver and spleen. The icterus index was 52 and the van den Bergh reaction was immediate direct with 70 mg of bilirubin per 100 cc of blood.

During the patient's stay in the hospital, the jaundice deepened, abdominal distention increased and the liver became palpable two fingers' breadth below the costal margin. He developed hiccoughs and paralytic ileus a few days before death, which occurred on February 10, 1934. The clinical diagnoses were obstructive jaundice, stone in the common bile duct, cholangitis and hepatitis.

*Autopsy*—Twelve hours after death. Dr. L. L. Lanyon. The gross anatomic findings were (1) Malignant duodenal ulcer surrounding the papilla of Vater, (2) marked dilatation of the common bile duct, (3) chronic cholecystitis, (4) calculous obstruction of the intrahepatic biliary radicles, (5) multiple liver abscesses confined mainly to the left lobe, (6) congestion and degeneration of the pancreas, (7) myocardial degeneration with passive congestion, and (8) cholemic nephrosis.

*Pathologic Examination*—The section of duodenum was lined by partially auto-lized mucous membrane, in the depths of which a malignant transformation was in progress. The atypical epithelial cells extended through the submucosa and muscular coats and were observed invading nerve fibers. The neoplastic cells varied considerably, with deeply acidophilic cytoplasm and hyperchromatic nuclei of varying size and shape, which were occasionally observed in mitosis. The cellular arrangement was in the form of nests, short cords and acini, the latter being frequently lined by tall

columnar cells with dark blue, basally situated nuclei. The connective tissue stroma was rather scanty and contained collections of lymphocytes.

A single section through the pancreas and common bile duct disclosed invasion of both these structures by tumor tissue. In other sections from the pancreas there was a moderate amount of fibrosis and inflammatory cell reaction about the ducts and within the lobules.

The liver tissue showed few of the features of biliary stasis, with little or no bile pigment present. In the inner portions of the lobules there was considerable sinusoidal congestion and degeneration and atrophy of the parenchyma. The hepatic cells showed active signs of regeneration with multiple nuclei and hyperchromasia. Peripherally there was a marked amount of fibrosis in and about the lobules and small abscesses were frequently observed.

**Case 4**—F T, colored, male, age 50, was admitted to the Philadelphia General Hospital February 10, 1933, complaining of stomatitis, marked jaundice and loss of weight. Over a period of years the patient had had digestive disturbances and for the last 18 months had noticed dyspnea on exertion. The terminal illness was initiated, seven weeks before admission to the hospital, by salivation and intense itching followed a week later by dark urine, clay-colored stools and jaundice and later by stomatitis and considerable loss of weight. There had been no constipation or unusual digestive disturbances at this time.

*Physical Examination* showed the spleen and liver to be both enlarged and pain was elicited on deep pressure over the liver. Roentgenographic studies disclosed a dense shadow in the region of the gallbladder, the stomach appeared hypertonic and the duodenal cap irregular. Icterus index 165, van den Bergh reaction immediate positive with 17.6 mg of bilirubin per 100 cc of blood. *Clinical Diagnosis*—Metallic poisoning. The patient became gradually weaker and died February 27, 1933, with the clinical signs of localized peritonitis.

*Autopsy*—Thirteen hours after death. Dr. H. McCutcheon. The combined gross and microscopic diagnoses were: (1) Peripapillary adenocarcinoma of duodenum, (2) hydrohepatosis with marked jaundice, (3) obstruction of pancreatic ducts with marked fibrosis, (4) biliary pigmentation of kidneys and mild nephrosis, and (5) suppurative bronchopneumonia.

Upon opening the duodenum a retracted scar, presumably a healed ulcer, was observed on the mucous surface of the pyloric ring. The papilla of Vater was surrounded by a nodular, pale growth measuring 2 cm in diameter, which obstructed the common bile duct. Proximal to the lesion the biliary passages were enormously distended and clear, dark-yellow bile could be forced through the papilla by making pressure on the gallbladder. The liver weighed 1,730 Gm and was dark green with accentuated liver markings.

*Pathologic Examination*—The section of duodenum consisted on either side of a strip of partially autolyzed mucous membrane with a few Brunner's glands in the submucosa. In the center of the section there was a shallow depression, the base and margins of which exhibited a carcinomatous change, and beyond this was a large tumor nodule (Fig. 4). Upon approaching this lesion the epithelial cells of the mucous membrane became hyperchromatic and atypical in the deeper portions of the crypts. The glands became elongated and broke through the submucosa, spreading out laterally and deeply infiltrating all coats of the duodenum (Fig. 5). As a rule the tumor cells were tall columnar, fairly regular and arranged in elongated acini with a lining one to several layers thick. The nuclei occupied a basal situation in these cells and there were approximately one or two mitotic figures per high power field. There were a few other acini which were small, round or imperfectly formed and lined by polyhedral or flattened cells which were frequently necrotic and desquamated. There was little tendency for the cells to grow in the form of clumps or nests. The supporting stroma was of adult connective tissue, relatively avascular, rather scanty in amount and infiltrated

## DUODENAL CARCINOMA

with small round cells. Chronic inflammatory changes were observed in the subserosa over a considerable distance.



FIG 4—Case 4. A section of duodenum showing hyperplastic changes in the mucous membrane and terminating in a large neoplastic nodule to the left (X10)

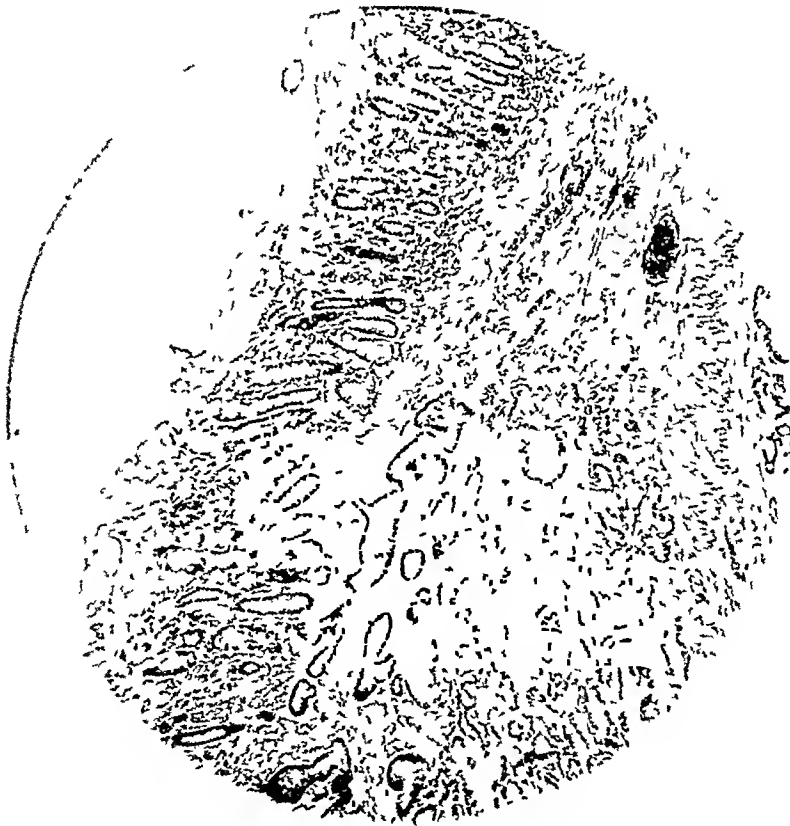


FIG 5—Case 4. Duodenum showing point of malignant transformation. The glands are elongated and have broken through the submucosa to infiltrate deeply all coats of the bowel (X40)

The characteristic features of biliary stasis were observed in the liver with pigmentation and degeneration about the central and sublobular veins and focal midzonal and biliary necroses. The portal radicles were moderately thickened by an eosinophilic and

round cell infiltration and proliferation of fibrous tissue and small biliary ducts. The variation in the appearance of the nuclei in the inner portion of the lobule suggested a rather marked degree of hepatic cell regeneration but no mitotic figures were observed. There was marked biliary pigmentation of the renal tissue and a mild grade of nephrosis.

The head of the pancreas was infiltrated with lymphocytes, mononuclear cells and connective tissue mainly peri-artery, perilobular and periductal in distribution. There was an associated atrophy and distortion of the acini and some proliferation of the ductal epithelium. A few ducts were dilated, lined with flattened epithelial cells and filled with a finely fibrillar, faintly eosinophilic material.

**Case 5**—F. C., white, female, age 82, was admitted to the Philadelphia General Hospital September 18, 1931, suffering from abdominal pain, jaundice, anorexia, emaciation and dehydration. The onset had occurred three weeks previously with severe, intermittent pain in the right upper abdominal quadrant. This was soon followed by deep jaundice.

*Physical Examination* demonstrated tenderness in the right upper abdominal quadrant and the liver was palpable four fingersbreadth below the costal border. Icterus index was 280, the van den Bergh reaction was immediate direct and there were 24 mg of bilirubin per 100 cc of blood. Death occurred October 1, 1931.

*Autopsy*—Five hours after death Dr. H. L. Stewart. The combined gross and microscopic diagnoses were: (1) Peripapillary carcinoma of the duodenum with extension to the pancreas and surrounding adhesions and with metastases to the liver and a regional lymph node, (2) hydrohepatosis with marked cirrhosis and jaundice, (3) calculous cholecystitis with obliteration of the cystic duct, (4) obstruction of duct of Wirsung, (5) biliary pigmentation of the kidney with marked nephrosis, and (6) acute degeneration of the myocardium.

The stomach, duodenum, pancreas, liver and gallbladder were tightly bound together by dense adhesions. Upon opening the duodenum, the papilla of Vater was found to be surrounded and obstructed by a large, firm fungating mass composed of smaller nodules which were yellow and white when incised. This tissue extended through the wall of the duodenum to infiltrate the pancreas and surrounding adhesions. The duct of Wirsung measured 1.5 cm in diameter. The common bile duct measured 7 cm in circumference and contained thin yellow, mucus-like fluid. The nodular lesions surrounding the papilla of Vater extended for a distance of 4 cm into the common bile duct. The cystic duct was obliterated. The gallbladder was markedly thickened and tightly contracted around two large, nonfreely, finely granular calculi; it contained no bile. The liver was nodular and mottled yellow and black. It cut with increased resistance exposing a surface composed of small nodules which had replaced the normal structure of the organ. In addition there were several nodular lesions throughout the liver which measured approximately 2 cm in diameter and presented the same appearance as the tissue about the papilla of Vater. Similar areas were observed in a lymph node at the junction of the common and cystic ducts.

*Pathologic Examination*—The section passed through the terminal portion of the common bile duct and a piece of underlying pancreas. The mucosa of the common bile duct was thickened and thrown into plump papillary projections composed of anaplastic epithelial cells which penetrated through the wall of the common bile duct into the pancreatic tissue. These cells were round or polyhedral, with pale, fairly smooth cytoplasm and large irregular hyperchromatic nuclei, such as are occasionally observed in mitosis. They grew in the form of strands, cords, clumps and small irregular acini and, in large areas, were totally necrotic. Perivascular and perineural infiltration was noted. The connective tissue stroma was relatively abundant, comparatively avascular, occasionally hemorrhagic, and infiltrated with small round cells. In some areas the tumor cells bore a striking resemblance to the squamous cell type but definite pearl formation and prickle cells were not observed.

The pancreatic tissue was extensively infiltrated with tumor cells. It also showed perilobular and peri-acinar fibrosis, dilatation of ducts and, in large areas, necrosis.

The kidney showed nephrosclerotic changes with a moderate grade of nephrosis and slight biliary pigmentation.

**Case 6**—K. M., white, female, obese, age 62, was admitted to the Philadelphia General Hospital August 28, 1932, complaining of weakness, loss of 40 lbs (18.1 Kg) over a period of six months and, latterly, nausea, vomiting and jaundice. There had been two episodes of painless jaundice lasting a week or ten days, one and three years previously. Jaundice had appeared three weeks before admission to the hospital and as it increased in intensity over a period of a week, there had developed pain, nausea, vomiting, fever, chills and clay-colored stools. The patient experienced several transitory painful seizures of a shooting character in the region of the gallbladder.

*Physical Examination* showed a very obese, elderly female with a definitely distended abdomen, there was no tenderness, rigidity or palpable masses, the liver and gallbladder were not palpable. The icterus index was 225, the van den Bergh reaction was immediate direct and there were 22.4 mg of bilirubin per 100 cc of blood. *Clinical Diagnosis*: Cholelithiasis, stone in the common duct. Vomiting continued, jaundice deepened progressively and death occurred, September 6, 1932.

*Autopsy*—Four hours after death. Dr. H. L. Stewart. The combined gross and microscopic diagnoses were: (1) Peripapillary carcinoma of the duodenum with extension into the pancreas and metastasis to liver, (2) hydropic hepatitis with marked jaundice, (3) obstruction of the duct of Wirsung, (4) calculous cholecystitis, (5) congestion and edema of lungs, and (6) acute myocardial degeneration.

The papilla of Vater was surrounded by a firm nodular papillary lesion which extended through the entire wall of the duodenum to invade the head of the pancreas for a short distance. The pancreatic and common bile ducts, although readily admitting the passage of a probe, were both obstructed, proximal to the papilla the bile ducts were enormously distended. The liver weighed 2,180 Gm and presented a deep green mottling. Two small firm button-like nodules 2 cm in diameter were present in the capsule. The intrahepatic biliary ducts were distended with bile-stained purulent fluid. The gallbladder was tightly contracted about a single soft calculus which measured 2 cm in diameter.

*Pathologic Examination*—The section of duodenum presented an unbroken autolyzed mucous membrane and scattered through all its layers were groups of atypical cells in acinar formation supported by a moderate amount of stroma. The majority of the tumor cells were well differentiated into tall columnar elements with basally situated hyperchromatic nuclei which were observed in mitosis, approximately once per high power field. Deeply, the tumor cells infiltrated a piece of attached pancreas for a short distance with, here and there, marked fibrosis and low grade inflammatory cell reaction with lymphocytes and mononuclear cells.

The hepatic tissue showed the features of early biliary stasis with pigmentation and degeneration in the inner portion of the lobules, focal midzonal areas of necrosis and early periportal fibrosis. Metastases were not observed in the sections of liver available for study.

The renal tissue was pigmented with bile and the tubular cells were degenerated.

**Case 7**—W. J., white, male, age 60, was admitted to the Philadelphia General Hospital, May 25, 1932, with profound jaundice and loss of 55 pounds (25 Kg) in weight. The illness began abruptly ten weeks previously with moderately severe, continuous epigastric pain which lasted for three weeks, at the end of which time it ceased completely, coincident with this there developed progressively deepening jaundice. The urine became dark and the stools clay-colored, but there was no nausea, vomiting or recurrence of abdominal pain.

*Physical Examination* did not demonstrate any palpable masses, tenderness or enlargement of the liver, there was, however, some fulness in the epigastrium. Roentgenographic

studies of the gastro-intestinal tract showed widening and stasis of the duodenal loop. There were 12 mg of bilirubin per 100 cc of blood and the van den Bergh reaction was immediate direct, the icterus index was 150.

A cholecystoduodenostomy was performed, June 28, 1932. The head of the pancreas was found to be enlarged and firm. The clinical manifestations of jaundice failed to abate following operation. The patient became gradually weaker and died, July 7, 1932.

*Autopsy*—Eighteen hours after death Dr W Brody. The combined gross anatomic and microscopic diagnoses were (1) Peripapillary carcinoma of the duodenum with metastases to the lymph nodes, (2) hydrohepatosis with marked jaundice, (3) obstruction of the duct of Wirsung and chronic pancreatitis, (4) hemorrhage into the lumen of the gallbladder and peritoneal cavity, (5) bile pigmentation and acute degeneration of the kidney, and (6) myocardial degeneration.

The body tissues were deeply jaundiced. There was moderate dilatation of the stomach and the peritoneal cavity contained 1,200 cc of bloody fluid which was believed to have originated from the operative wound in the neighborhood of the gallbladder. The papilla of Vater was surrounded and obstructed by a fungating ulcerated indurated lesion proximal to which the biliary passages were markedly distended, the common bile duct measuring 4 cm in circumference. The lumen of the gallbladder was completely occluded with clotted blood which effectually obstructed the flow of bile from the cystic duct into the duodenum through the cholecystoduodenostomy opening. The liver weighed 1,700 Gm, its cut surface was mottled deep green and studded with bile ducts filled with green bile. The duct of Wirsung admitted the passage of an ordinary pencil. The head of the pancreas was extremely firm and the tail contained numerous cysts, on section, the pancreatic tissue was lobulated and contained homogeneous areas throughout the gland, suggestive of neoplastic invasion. There was no mention of the lymph nodes in the protocol.

*Pathologic Examination*—The duodenum could not be positively identified in any of the sections available for study. In one section of autolyzed fibromuscular tissue (probably duodenum) and in several others containing lymph nodes there were actively invasive, atypical epithelial cells arranged in elongated acini and small, solid clumps. The cells were moderately anaplastic in some areas while in others they preserved many of the characteristics of intestinal mucous membrane, being arranged in single-layered rows of tall columnar cells with basally situated nuclei. In some of the elongated acini, the epithelial cells were heaped up forming short spur-like projections supported by a delicate stroma. The nuclei were irregular in places and hyperchromatic, with approximately two mitotic figures per high power field. A few small hemorrhages and several large areas of necrosis were observed.

The pancreas showed a marked increase in fibrous tissue, and lymphocytes in and around the lobules of the parenchyma, which was extensively atrophied.

The sections of liver presented the picture of marked biliary stasis. There was a marked grade of perilobular and intralobular fibrosis and proliferation of the smaller bile ducts.

There was biliary pigmentation of the kidney, marked nephrosis and thickening of the arterial branches.

**Case 8**—J B, white, male, age 74, was admitted to the Philadelphia General Hospital, July 7, 1931, suffering with abdominal pain, loss of appetite and deep jaundice. For years, the patient had had chronic, fibrous pulmonary tuberculosis with cavitation of both apices. His terminal illness began with loss of appetite, six months before admission to the hospital. During the next four months, he developed belching, vomiting after meals, and dull, constant abdominal pain. Icterus was first noticed six weeks before admission and gradually increased in intensity.

*Physical Examination* demonstrated some fulness and rigidity of the right hypochondrium but there were no definite masses and the liver was not palpable. Roentgenographic examination of the gastro-intestinal tract demonstrated hypoperistalsis and reten-

tion in the pyloric end of the stomach and first two portions of the duodenum. In the prone position there was a slight prepyloric irregularity. The conus and third portions of the duodenum were slightly dilated, and the first and second portions were displaced somewhat to the right and downward in a circular fashion. The patient grew progressively weaker and died, July 10, 1931.

*Autopsy*—Fifty-two hours after death. Dr. J. F. Cohen. The combined gross and microscopic diagnoses were: (1) Peripapillary carcinoma of the duodenum with lymph node metastases, (2) hydrohepatosis with marked jaundice, (3) calculous cholecystitis, (4) chronic fibrous pulmonary tuberculosis with cavitation, (5) myocardial degeneration and fibrosis, (6) degeneration and biliary pigmentation of the kidney with calcification of tubular epithelium, and (7) acute fibrinous peritonitis.

The peritoneal cavity contained 200 cc of brown, turbid fluid, the coils of intestine were adherent to each other and covered with bile-tinged, plastic exudate. The papilla of Vater was surrounded on all sides by a circular, ulcerative necrotic process, the margins of which were soft, round and elevated, while the base was firm and resistant to the touch. The intrapapillary portion of the duodenum was dilated, the stomach appeared normal. Proximal to the papilla, the common bile duct and hepatic ducts were dilated but the cystic duct was not involved in this process, the gallbladder was small, thick and fibrous and bound by adhesions to the colon and duodenum. The gallbladder was filled by a single, hard, cylindrical calculus, and in one area its mucous membrane was ulcerated. The liver appeared small, its surface was lobulated, mottled yellow and green, firmer than usual and apparently fibrotic. The pancreas was somewhat autolyzed. The lymph nodes appeared normal.

*Pathologic Examination*—The section of duodenum consisted of hyperplastic mucosa changing at one place into disorderly columnar cells arranged in acini which penetrated deeply into the submucosa. This section of duodenum showed advanced autolytic processes so that the following description of the neoplasm is based upon the findings in one of the lymph nodes. This node was largely replaced by groups of tall columnar epithelial cells arranged in elliptical acini, most of which were large and resembled somewhat the crypts of intestinal mucosa. The cells were usually arranged in a single layer but in places, mounds of four to 12 layers were observed. The characteristic cell had acidophilic cytoplasm and round to ovoid nuclei usually situated at the basal pole. The nuclei were moderately hyperchromatic, and two to three mitotic figures per high power field could be found in different parts of the section. The atypical epithelial cells invaded the capsule of the node and spread out into the surrounding fibrous tissue.

Sections of the liver showed bile casts and pigmentation, degeneration and necrosis of the hepatic cells in the inner portion of the lobule. In the portal radicles, there was an increase in fibrous tissue, an infiltration of lymphocytes and a moderate degree of proliferation of the bile ducts.

Sections of the kidney showed a moderate degree of nephrosis and pigmentation, and numerous small discrete and confluent masses of calcium were observed. The position of many of these calcific deposits could not be positively identified, but others definitely appeared to lie within tubules, some of which were completely calcified. Several of the larger arteries were thickened and sclerotic.

Sections of pancreas were not available for study.

**Case 9**—G. F., white, male, age 81, was admitted to the Philadelphia General Hospital, December 2, 1930, suffering from marked jaundice and intermittent chills and fever. The onset had occurred seven months previously, with chills and fever of the Charcot type and progressive, painless jaundice.

*Physical Examination* showed the abdomen to be protuberant, tense, and gave the physical signs of containing fluid. After removing 3,200 cc of clear, bile-stained fluid, the liver edge was palpable four fingers' breadth below the costal border. Roentgenographic studies of the gastro-intestinal tract were unsatisfactory because of the patient's



inability to ingest sufficient barium *Clinical Diagnosis* Carcinoma of the head of the pancreas The patient became gradually weaker and died, December 20, 1930

*Autopsy*—Two hours after death Dr H Gunn The combined gross and microscopic diagnoses were (1) Peripapillary adenocarcinoma of duodenum, (2) hydrohepatosis with atrophy and fibrosis of gallbladder, cirrhosis of liver and marked jaundice, (3) obstruction of the duct of Wirsung with pancreatic fibrosis and fatty infiltration, (4) arterionephrosclerosis with parenchymatous degeneration and biliary pigmentation, and (5) myocardial fibrosis

All the tissues were jaundiced and there were 1,500 cc of straw-colored fluid in the peritoneal cavity About 3 cm above the papilla of Vater, a small nodule was found in the wall of the duodenum which, on section, proved to be cystic and contained milky fluid (minor papilla?) The papilla of Vater was surrounded by a cauliflower-like growth 3 cm in diameter composed of firm papillary masses, finely granular in texture The pancreatic duct opened into this mass and was dilated throughout its entire length The glandular tissue of the pancreas was atrophic and largely replaced by fat The bile ducts proximal to the papilla were greatly distended but the gallbladder was shrunken and atrophied The liver weighed 1,560 Gm, it was green and coarsely nodular and on section, the bile ducts were found to be dilated and filled with coarse debris

*Pathologic Examination*—The section of the duodenum contained a small area in which the mucous glands became somewhat atypical with hyperchromasia and irregularity of the epithelial cells, these penetrated into the submucosa and muscularis for a short distance Another section of duodenum was covered with a narrow strip of hyperplastic mucous membrane which merged into an area of well differentiated papillary adenocarcinoma The acini of the tumor were composed of oval, elongated crypts resembling closely the normal mucous membrane and they extended through all coats of the intestinal wall The atypical cells were usually piled up in several layers on the walls of the acini and consisted of tall columnar elements with basally situated nuclei varying somewhat in size and shape but staining fairly uniformly From two to six mitotic figures were observed per high power field The stroma was not abundant, it contained numerous congested blood vessels, many of which were poorly developed, and was infiltrated with many lymphocytes

The hepatic cells were intensely pigmented, moderately degenerated, loosened from the reticulum about several of the bile ducts and exhibited some evidences of regeneration in the inner portion of the lobule There was a moderate degree of small bile duct proliferation and the portal areas were markedly thickened by fibrous tissue which extended into the periphery of the lobules, isolating hepatic cells singly and in small groups

In a section of pancreas from the region of the common bile duct, the interstitial tissue was distributed abundantly about the lobules and acini and the associated parenchymal cells were markedly atrophied

There was a moderate grade of nephrosclerosis with acute congestion and several small retention cysts The tubular epithelium was slightly pigmented and showed rather marked degeneration and necrosis

There was considerable interstitial fibrosis of the myocardium

*Case 10*—L E, colored, male, age 56, was admitted to the Philadelphia General Hospital, August 27, 1930, in a semiconscious state, and no history was obtainable

*Physical Examination* showed a well rounded mass, continuous with the liver, in the right upper abdominal quadrant and extending 6.5 cm below the costal border There was no abdominal rigidity, tenderness or evidences of fluid *Clinical Diagnosis* Chronic nephritis, chronic myocarditis and uremia Two days after admission, the patient lapsed into coma and died

*Autopsy*—Four hours after death Dr W H Black The combined gross and microscopic diagnoses were (1) Peripapillary carcinoma of the duodenum with metastasis to a regional lymph node, (2) hydrohepatosis with marked jaundice, (3)

obstruction of the duct of Wirsung and chronic pancreatitis, (4) arteriosclerosis of the aorta and coronary arteries, and (5) severe biliary nephrosis

The papilla of Vater was surrounded by a ring of indurated tissue which on section was white, opaque and appeared neoplastic. By exerting pressure on the gallbladder, bile could be forced through the orifice of the papilla which admitted a probe with difficulty. Proximal to the obstruction the biliary passages were markedly distended, the common bile duct measured 5.5 cm in circumference, the hepatic duct 4.5 cm and the cystic duct 3 cm. The gallbladder extended to the level of the umbilicus, its wall was thin and its lumen was distended with pale-green bile and "biliary mud." The liver measured 34x23x7 cm and extended a hand's breadth below the costal margin. It was deeply bile-stained with prominent lobular markings and a thickened capsule over the gallbladder fossa.

The pancreas was indurated. The duct of Wirsung was dilated to a circumference of 3 cm. The duct of Santorini opened 2 cm above the papilla of Vater. The stomach contained a considerable quantity of blood and its mucous membrane was thrown into prominent rugae dotted with petechial hemorrhages.

The kidneys were enlarged, weighing respectively 380 and 360 Gm. They were swollen, soft, grass-green in color and regular in outline. The capsules were adherent in a few places, the cut surface was mottled red and green with small greenish-black, punctate areas in the cortex.

The lymph nodes were large, soft and greenish-black.

*Pathologic Examination*—The section of duodenum consisted of smooth muscle overlaid with submucosa containing Brunner's glands and above these a small remnant of partially autolyzed mucous membrane. Deeply, the mucosa merged into an area of immature epithelial cells which penetrated through the submucosa into the muscularis. These atypical epithelial cells were small, polyhedral and columnar in shape and tended to be arranged in acini, short rows and small nests of from one to several dozen cells embedded in dense connective tissue. The cytoplasm was acidophilic and the nuclei were hyperchromatic, basally situated in the columnar cells but occupied no characteristic position in the other cells.

The liver presented the picture of biliary stasis with associated pigmentary and regressive changes around the central and sublobular veins. No biliary or focal midzonal areas of necrosis were observed. There was a marked increase of connective tissue, predominately periportal but in some places diffuse and was most marked about the bile ducts. There was very little proliferation of the smaller bile ducts.

Sections of the pancreas showed marked perilobular and diffuse, hyalinized fibrosis with marked atrophy of the parenchyma.

The kidney sections showed marked bile pigmentation.

A section of a lymph node showed a metastatic tumor nodule with the characteristics of the primary lesion.

**Case 11**—W. R., colored, male, age 65, was admitted to the Philadelphia General Hospital, July 9, 1928, suffering from jaundice, obstipation and incessant vomiting, which had begun two weeks previously. The patient was markedly dehydrated, weak and emaciated.

*Physical Examination* demonstrated epigastric resistance, there were no masses palpable. Icterus index 12. The van den Beigh reaction was delayed. *Clinical Diagnosis*—Intestinal obstruction either from intussusception or volvulus.

*Autopsy*—Eight hours after death. Dr. D. R. Morgan. The combined gross anatomic and microscopic diagnoses were: (1) Peripapillary adenocarcinoma of the duodenum with metastasis to the liver, (2) hydrohepatosis with jaundice, (3) chronic pancreatitis, (4) cardiac hypertrophy with myocardial degeneration and fibrosis, and (5) congestion and edema of lungs.

The papilla of Vater was much thickened, firm and constricted, although bile could be forced through it into the duodenum by exerting pressure upon the gallbladder.

Proximal to the papilla, the extrahepatic biliary passages were all greatly dilated, the gallbladder being somewhat thickened, hyperemic and distended with dark, thick bile.

The liver, weighing 1,600 Gm, was dark and mottled in appearance and contained three slightly elevated pea-sized nodules on the surface. The lymph nodes along the course of the bile ducts were enlarged and firm. The pancreas appeared firm and fibrotic.

*Pathologic Examination*—Two sections of the duodenum were available for microscopic study. In one of these, there was an extensive carcinomatous infiltration of the submucosa but the mucous membrane and Brunner's glands were uninvolved. In the other, there was extensive ulceration of the mucous membrane and beneath this, neoplastic cells permeated the nodules of Brunner's glands. It was not possible to determine whether or not the carcinomatous cells arose from intestinal epithelium. The neoplasm extended into the muscular coat in long strands, circular nests and elongated and branching cords supported by a scanty stroma supplied with well formed vessels. The cells grew, principally, in the form of solid masses but an imperfect attempt to reproduce glandular structure was common and occasionally acini were observed, with a single layer of tall columnar epithelium with basally situated nuclei suggesting an intestinal origin. In the closely packed nests, cell outlines were practically indistinguishable, the cytoplasmic masses appearing as syncytial structures in which the nuclei were hyperchromatic, but only a few mitotic figures were found. There was very little necrosis and hemorrhage.

Sections of the liver showed the characteristic picture of bile stasis with pigmentation of the hepatic and Kupffer cells in the inner portion of the lobules with associated degeneration and necrosis of the parenchyma and with congestion of the sinusoids. The portal radicles showed a marked increase in connective tissue and small bile duct proliferation and a low grade chronic inflammatory reaction. In one portion of the section there was a nodule of neoplastic cells resembling those described above.

There was no evidence of carcinomatous invasion of the pancreas, even in those areas attached to the portions of the duodenum in which there was neoplastic infiltration of its musculature. A low grade lymphocytic reaction and marked fibrosis were observed through the pancreatic tissue.

There were marked biliary pigmentation of the kidney and a moderate grade of nephrosis with congestion.

*Case 12*—J. W., white, female, age 59, was admitted to the Jefferson Hospital, October 10, 1927, complaining of slight jaundice, belching, weakness, gastric distress, pain in the back and loss of 50 pounds (22.7 Kg). She recalled having had occasional attacks of indigestion which were not associated with pain or jaundice, laterally, she had noticed some edema of the ankles, especially at the end of the day. Her terminal illness developed suddenly, in December, 1926, with symptoms suggestive of acute food poisoning followed by a persistent feeling of distress in the region of the stomach, which was accentuated by taking food. A month later, jaundice appeared and deepened progressively, the stools became clay-colored and remained light until two weeks before admission. At about this time she experienced persistent pain in the back, and there ensued a gradual enlargement of the abdomen.

*Physical Examination* showed the abdomen to be distended with fluid. It was extremely tender in the epigastric region. The edge of the liver was palpable 8 cm. below the costal margin in the midclavicular line. The gallbladder was not visualized in the roentgenologic studies. Fluoroscopic examination of the gastro-intestinal tract following a barium meal, January 21, 1927, showed rapid filling of the stomach but peristalsis was not active during the first few minutes. The fundus of the stomach was situated four fingers' breadth below the iliac crest. An elongated and dilated duodenal bulb was visualized and, although no defect of the bulb could be determined, it was felt that its configuration was suggestive of some pathologic change. *Clinical Diagnosis* Carcinoma of the head of the pancreas or gallbladder disease. The patient became gradually weaker and died, October 19, 1927.

*Autopsy*—Eight hours after death Dr B L Crawford The combined gross and microscopic diagnoses were (1) Peripapillary adenocarcinoma of the duodenum with extension into the pancreas and mesentery, metastases to the liver and lymph nodes, (2) marked dilatation of the extrahepatic bile ducts and calculous cholecystitis, (3) dilatation of the pancreatic ducts and chronic pancreatitis, (4) hemoperitoneum, originating probably from a rupture of the liver, and (5) chronic nephritis with arteriosclerosis

The skin was pale and sallow but not definitely jaundiced, the peritoneal cavity contained 2,500 cc of unclotted blood, and the greater part of the upper half of the abdomen on both sides was occupied by an enormously enlarged liver The stomach was distended with greenish fluid

At the papilla of Vater there was a soft, round, somewhat necrotic nodule in the wall of the duodenum which was elevated 2 cm above the surface and measured 3 cm in diameter The common bile duct opened into the center of this nodule and bile could be expressed through the orifice, which readily admitted the passage of a probe all the way through into the gallbladder The head of the pancreas was densely adherent to the duodenum opposite the lesion but, as far as could be ascertained, it was not extensively involved by tumor tissue Many regional lymph nodes, in and behind the peritoneum and about the liver and pancreas, were firm, gray and enlarged The liver weighed 3,970 Gm and was firm, mottled, uniformly enlarged, and slightly nodular on the surface On section, soft, gray nodules of tumor tissue were found to be embedded in a relatively small amount of residual hepatic tissue, which was firm, friable and hemorrhagic and cut easily Beneath the capsule, in one area in the left margin, there was a rupture of the liver substance 2 cm in length, which was considered the probable source of the hemoperitoneum The gallbladder was thickened and contained a small amount of dark green bile together with several large, irregular, dark green calculi A finger was readily introduced into the common bile duct up to its point of entrance into the mass surrounding the papilla of Vater

*Pathologic Examination*—The section of the duodenum consisted, at one end, of intestinal mucous membrane and underlying this a thick muscular wall which gradually tapered off and disappeared at the opposite end of the section Beginning at the wide border and following along the surface of the section, the mucous membrane became gradually thicker, coincident with the development of a patchy malignant change in the form of nests of atypical epithelial cells in the deeper mucosa and submucosa The lining of the intestine expanded into a broad papillary projection which, after partially encircling the narrowed end of the muscular coat, became atrophic, autolyzed and villous-like, and resembled the epithelium of the common bile duct The neoplastic lesion consisted of nodules and large acini composed of papillary projections with relatively few cells embedded in considerable quantities of mucinous material The underlying muscular coat was infiltrated with small clumps of columnar or polyhedral, acidophilic, vacuolated cells surrounded by slender basophilic mucinous strands The nuclei were usually hyperchromatic, variable in size and shape, basally situated in the columnar cells and not observed in mitoses The supporting stroma was relatively scanty and rather avascular

The pancreatic tissue was infiltrated with tumor cells and showed dilatation of the ducts and extensive fibrosis Metastatic lesions were observed in the lymph nodes, mesentery and liver, and showed infiltration of nerves and blood vessels and extensive hemorrhage and necrosis The hepatic tissue was congested in the inner portion of the lobules and compressed and atrophied about the tumor nodules

*Case 13*—E S, white, female, age 79, was admitted to the Philadelphia General Hospital, December 19, 1926 The onset of her illness had occurred six months previously with jaundice, clay-colored stools and itching, and later on, diarrhea, nocturia and inability to lie prone in bed There was no history of weight loss

*Physical Examination* showed a slight abdominal distention, on deep inspiration a small mass was palpable, which descended from the edge of the liver in the right upper quadrant of the abdomen Roentgenologic studies of the gastro-intestinal tract disclosed

what was interpreted as the presence of a lesion extrinsic to the stomach and duodenum  
*Clinical Diagnosis* Carcinoma of the pancreas and bile ducts Death occurred, December 26, 1926

*Autopsy*—Ten hours after death Dr F W Konzelman The combined gross anatomic and microscopic diagnoses were (1) Adenocarcinoma of the region of the papilla of Vater, (2) hydrohepatosis with marked jaundice, (3) dilatation of pancreatic ducts and chronic interstitial pancreatitis, (4) bronchopneumonia, (5) dilatation of heart with acute myocardial degeneration, (6) arteriosclerosis of aorta, coronary arteries and renal arteries, and (7) nephrosis

The peritoneal cavity was bile-stained and contained a small amount of yellowish fluid Upon opening the duodenum the papilla of Vater was found encircled by indurated



FIG 6—Case 13 Ampulla of Vater showing a malignant change in the tips of the villi The atypical epithelial cells extend deeply into the wall of the duct (X40)

tissue There was no ulceration and the lesion involving the papilla did not project into the lumen of the intestine The ampulla of Vater was apparently not examined Proximally, the biliary passages were enormously distended and contained a large amount of watery, green bile The liver, weighing 2,950 Gm, was tough and fibrous, and showed a finely granular green surface The cut surface was mottled with fine green and yellow markings

*Pathologic Examination*—A section was obtained for histologic study which passed through the duodenum and included the ampulla of Vater One side of the ampulla appeared normal except for autolysis of the epithelial lining cells At one point a malignant change was observed in the tips of the villous projections and on the surface Here the atypical epithelial cells were piled up forming a thick plaque without definite ulceration (Fig 6) The tumor tissue extended through the wall of the duct into all coats of the surrounding duodenum, permeating, only slightly, however, into the autolyzed duodenal mucous membrane in its deepest portion The neoplastic cells were well differentiated, tall columnar elements with acidophilic granular cytoplasm and basally situated nuclei A few of the cells were irregular in size, shape and staining, and had enlarged hyper-

chromatic lobulated nuclei. Mitotic figures were infrequently observed and had a regular appearance. Most of the atypical cells were arranged in small round glandular structures but in places the acini were large and elongated with hyperplastic lining cells. In a few places the tumor cells grew in nests and irregular cords. The stroma was composed of mature connective tissue which was relatively scanty, avascular and infiltrated with small round cells and polymorphonuclear leukocytes, especially where the tumor tissue was necrotic.

The lungs showed bronchopneumonia, congestion and edema.

The pancreas showed dilatation of the ducts and diffuse and perilobular fibrosis. The parenchymatous tissue was somewhat atrophied, but the islands of Langerhans were well preserved and there were practically no inflammatory cells.

The kidneys showed a moderate grade of nephrosis and slight bile pigmentation.

The liver showed the well advanced changes of biliary stasis with pigmentation and degeneration in the inner portion of the lobule, focal midzonal necroses, proliferation of the small bile ducts, fibrosis of the portal radicles and marked associated inflammatory reaction.

**Case 14**—W. H., colored, male, age 77, was admitted to the Philadelphia General Hospital, November 11, 1926, with marked jaundice. The only history obtainable was that the patient had been sick for two years with indefinite epigastric pain, weakness and loss of weight. The exact time at which jaundice appeared could not be determined.

*Physical Examination* showed a large, tender, immovable mass, palpable in the epigastrium just below the costal margin and a little to the right of the midline. The patient was found dead in bed, November 14, 1926.

*Autopsy*—Twenty-four hours after death. Dr. E. Wiess. The combined gross anatomic and microscopic diagnoses were: (1) Peripapillary adenocarcinoma of the duodenum with extension to the pancreas, (2) hydrohepatosis with suppurative cholangitis and marked jaundice, (3) obstruction to the duct of Wirsung and chronic pancreatitis, (4) myocardial degeneration, (5) arteriosclerosis of the kidneys with bile pigmentation and nephrosis, and (6) fibrocaseous tuberculosis of the lymph nodes.

The stomach was dilated and contained bile-stained, slimy mucus. The site usually occupied by the papilla of Vater was marked by an elevated, ulcerated, congested lesion which was directly continuous with a large tumor mass in the head of the pancreas. Proximal to the lesion, the duct of Wirsung and the biliary passages were enormously distended. The gallbladder measured 16x8 cm and was filled with milky fluid. The intrahepatic biliary ducts were distended and the liver was tense and finely mottled. Many of the regional lymph nodes were firm and white.

*Pathologic Examination*—There were areas of acute inflammation and ulceration in the mucous membrane of the duodenum. Atypical epithelial cells supported by a moderate amount of stroma blended in places with the mucosal cells and extended into the deeper layers of the section. For the most part they were arranged in small, round or larger, irregular acini, a few of which resembled crypts of intestinal mucosa in having a single layer of tall columnar epithelium with deeply placed polar nuclei. Generally, however, the cells were poorly differentiated, of irregular shapes and varying sizes and tended to be massed into nests. The nuclei were oval, round, large and irregular, many of them were hyperchromatic and contained prominent nucleoli and a few were seen in mitosis. The tumor was vascular, with many immature blood vessels. There were large areas of hemorrhage, necrosis and suppuration, especially near the surface. The deeper portion of this section was continuous with a large, necrotic tumor mass in which pancreatic tissue was not identified.

A section of pancreas contained several dilated ducts which were lined by irregular tall columnar epithelium thrown into small folds. There was marked atrophy of the parenchymatous tissue of the pancreas and a diffuse proliferation of fibrous tissue markedly infiltrated with lymphocytes. The islands of Langerhans survived the atrophic process and appeared to be relatively numerous.

The liver showed marked bile stasis, with the usual pigmentation and necrosis in the inner portion of the lobule, biliary and focal midzonal necroses and bile duct proliferation, fibrosis and marked chronic suppurative inflammatory reaction in the portal areas.

The kidney showed bile pigmentation and a moderate degree of nephrosis.

Section of a lymph node showed extensive, fibrosing miliary tuberculosis. Sections of the lung were not available for study.

**Case 15**—J. M., white, male, age 46, was admitted to the Philadelphia General Hospital, May 22, 1933, after an illness of two months' duration. At the onset there were cough, loss of appetite and edema of the extremities, ten days before admission, jaundice and clay-colored stools and a loss of 20 pounds in weight (9 Kg.) were noted.

*Physical Examination* showed abdominal distention and a palpable mass in the right upper quadrant, with fulness and resistance over the gallbladder area. Following the removal of 3,300 cc. of dark, amber fluid from the peritoneal cavity, several nodules became palpable in the right upper quadrant. Roentgenologic studies revealed the contours of the stomach normal in the erect position with slight displacement of the organ to the right. Peristaltic movements passed uninterruptedly along both curvatures. The cap appeared normal, but there was widening of the duodenal loop and considerable stasis in the second and third portions. There was no evidence of metastatic deposits in the lungs. The roentgenologic conclusion was that the stomach and duodenum were negative. The icterus index was 50 and 60, respectively, on two occasions. There was a biphasic van den Berg reaction and 35 mg. of bilirubin per 100 cc. of blood. The patient developed paranoid delusions and died, June 12, 1933.

*Autopsy*—Twenty-two hours after death. Dr. H. Lund. The combined gross anatomic and microscopic diagnoses were (1) Carcinoma of the ampulla of Vater with extension through the wall of the duodenum into the pancreas, (2) suppurative hydro-hepatosis with marked jaundice, (3) obstruction and suppurative inflammation of the duct of Wirsung with chronic pancreatitis and peripancreatic fat necrosis, (4) bronchopneumonia, and (5) renal arteriosclerosis and marked nephrosis.

There was moderate distention of the stomach and proximal half of the duodenum. The papilla of Vater consisted of a smooth, light yellow, fluctuant nodule which projected for a distance of 1 cm. into the lumen of the duodenum. The immediately surrounding tissue was quite firm. The orifice of the common bile duct was situated on the under surface of this nodule near its junction point with the duodenal mucosa. A probe was readily passed into the ampulla which, when opened, disclosed the presence of a small, pink polypoid lesion projecting 0.15 cm. above the level of the mucous membrane. Proximal to this lesion the common bile duct was dilated to a diameter of 3.6 cm., the gallbladder formed a greatly distended, thin-walled sac measuring 16×7×4.5 cm., and contained flaky yellow fluid.

The liver weighed 1,700 Gm., it was firm, green, cut with increased resistance and disclosed marked distention of the intrahepatic bile ducts. Small, yellow flake-like areas, 2 cm. in diameter, were observed in the hepatic parenchyma near the hilus.

The pancreas was much firmer than normal and cut with increased resistance, disclosing marked distention of the duct of Wirsung throughout its entire course. This duct measured 2.5 cm. in the tail of the pancreas and 3.5 cm. in the head.

*Pathologic Examination*—The small polypoid nodule observed in the ampulla of Vater consisted of cells in disorderly arrangement but tending to form crypts and acini (Fig. 7). The nuclei varied in size and shape, some attaining a very large size. They showed some evidence of biliary autolysis but in spite of this stained more intensely basophilic than would be expected. No mitotic figures were observed. The atypical epithelial cells were supported by a central stroma consisting of a few strands of fibrous tissue which branched near the base to form a polyp consisting of two small finger-like processes. The base merged at right angles into a zone of smooth muscle with no characteristic arrangement. The epithelial cells described above penetrated in small strands and clumps into this muscular tissue.

The common bile duct was markedly thickened and its mucosa was autolyzed and stained with bile. No evidences of carcinoma were observed.

The duodenum had a moderately hyperplastic mucosa, its muscular wall was thickened and in the deeper portions, strands of small atypical epithelial cells, tending to be arranged in single layer rows, penetrated between the bundles of smooth muscle from the side opposite the mucosa.

A section of the pancreas adjoining the common bile duct showed similar small atypical epithelial cells arranged in rows a single layer deep. These cells tended to be polyhedral, formed elliptical acini, and closely resembled the cells in the ampullary polyp.

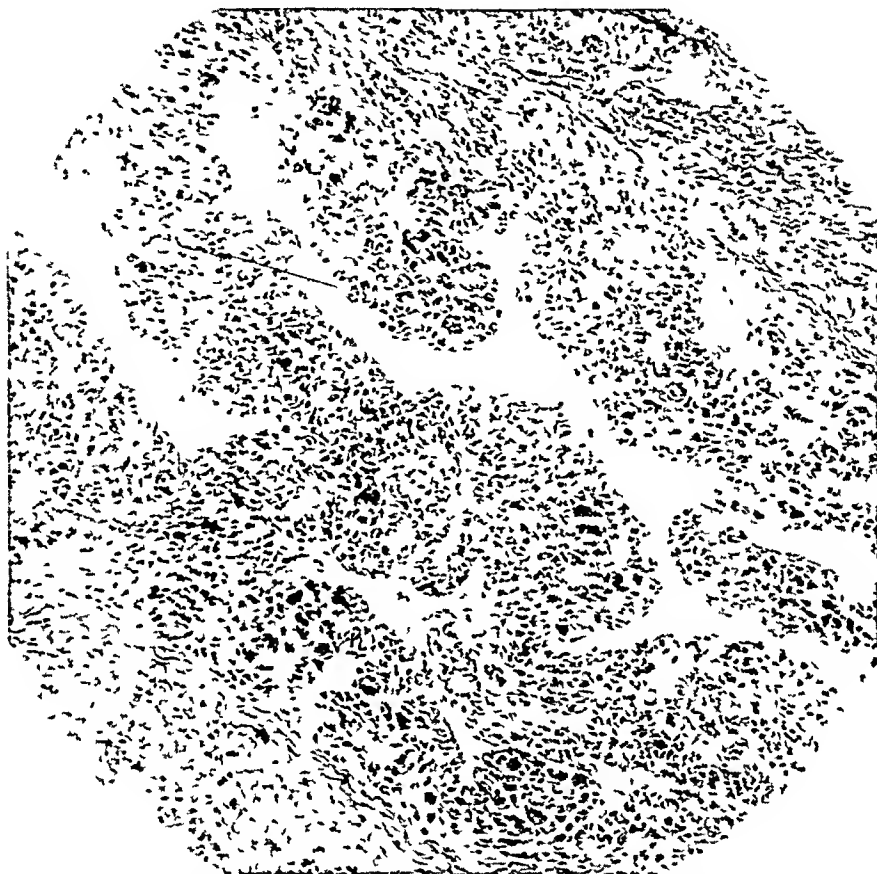


FIG 7—Case 15. Lumen of ampulla of Vater almost filled with broad papillary projections of the malignant polyp with infiltration of the surrounding tissues (×100).

without, however, showing as much variation in the size of the nuclei. Sections from various other portions of the pancreas showed parenchymal atrophy, interstitial fibrosis and suppurative inflammation of the ducts.

The liver showed characteristic evidences of long-standing obstruction, with pigmentation, degeneration and atrophy of the cells about the central and sublobular veins, biliary and focal midzonal necroses and marked fibrosis about the portal radicles. The sinusoids were distended and there were numerous small abscesses observed near the portal radicles and beneath the capsule of the liver. The hepatic parenchyma showed only slight evidences of regeneration and no mitotic figures.

**Case 16**—G. P., white, female, age 45, was admitted to the Jefferson Hospital, August 9, 1937, complaining of itching, jaundice, pain in the back and loss of weight. The patient had always been in good health until seven weeks previously when she had generalized itching and slight chills. Jaundice appeared two weeks later with very dark urine and clay-colored stools. At this time, there was also pain in the lower thoracic



region of the back and a feeling of soreness in the right upper quadrant of the abdomen. The pain increased in severity, becoming continuous and, at times, there was radiation to both shoulder blades. Nausea and vomiting occurred on several occasions. The jaundice deepened progressively although, during the last two weeks, the stools had become brown and jaundice had diminished somewhat in intensity. The appetite was poor and there was a loss of 25 pounds (11 Kg). The temperature was septic in type and varied from 99.5° to 104° F.

*Physical Examination* demonstrated a firm, irregular, tender mass which descended on inspiration to the level of the umbilicus, and which occupied the epigastrium and right upper quadrant of the abdomen. The duodenal content was blood-tinged and contained a small quantity of bile on the first examination, one week later, however, it had become bloody and did not show any bile on two examinations. The gallbladder was not visual-



FIG 8—Case 16. Opened papilla of Vater and common bile duct. Note the granular polypoid lesion in the terminal 1.3 cm, and the widely dilated ducts and gallbladder (X15).

ized in the cholecystographic studies. Roentgenologic studies of the gastro-intestinal tract showed a normal stomach and duodenum and no abnormal retention of barium. The van den Bergh reaction on the blood was positive direct with 14 mg per cent of bilirubin. Test of liver function with bromsulfalein showed 100 per cent retention of the dye in 30 minutes (2 mg dosage).

On August 22, 1937, the patient vomited dark blood and passed several tarry stools. Bleeding from the gastro-intestinal tract continued. The course of the disease was increasingly downward, in spite of blood transfusions, totaling 2,500 cc during the following six days. *Clinical Diagnosis*: Impacted stone in the common bile duct or carcinoma of the head of the pancreas. Death occurred, August 29, 1937.

*Autopsy*—Ten hours after death Dr M. M. Lieber. The combined gross and microscopic diagnoses were: (1) Adenocarcinoma, primary in the region of the ampulla of Vater, with extension to the head of the pancreas and metastases to liver, (2) hydro-hepatosis with marked jaundice, (3) obstruction of the duct of Wirsung with chronic pancreatitis, (4) biliary pigmentation of the kidney and moderate nephrosis, (5) bronchopneumonia, (6) acute myocardial degeneration and sclerosis of mitral and aortic valves, and (7) atherosclerosis of coronary arteries and aorta.

The stomach was distended with 250 cc of fluid and partially digested food rem-

nants The intestinal tract contained free blood and blood-tinged mucus The proximal segment of the second portion of the duodenum was densely adherent to the hilum of the liver The papilla of Vater projected into the duodenum as a soft, cylindro-conical body 3 cm long and 2.5 cm in diameter A probe easily passed through the orifice on the apex of the papilla and was followed by a flow of greenish-black bile The intestinal mucous membrane covering the papilla was smooth, not thickened and freely movable On opening the bile ducts and papilla of Vater, a sharply demarcated, soft, granular polypoid lesion, without ulceration, was found in the terminal 13 cm (Fig 8) The orifice of the duct of Wirsung was obscured, retrograde probing of the dilated duct met with an absolute obstruction in the head of the pancreas adjacent to the primary lesion The duct of Santorini was patent and opened into the duodenum 2 cm proximal to the papilla of Vater Proximal to the primary lesion, the biliary ducts and gallbladder were moderately distended The regional lymph nodes were slightly enlarged and soft and did not appear to contain any neoplastic tissue

The gallbladder projected 3 cm below the inferior margin of the liver and was filled with 60 cc of greenish-black bile, no calculi were found, its wall was moderately thickened

The liver weighed 2,000 Gm The surface was smooth except for varicose biliary ducts and two small, circumscribed, yellowish-gray metastatic nodules in the right lobe The cut surface was grass-green and the biliary ducts were markedly distended and filled with green bile

The pancreas was firm and cut with a grating sensation, disclosing perilobular fibrosis, fatty infiltration and atrophy of the parenchyma There were no evidences of neoplastic infiltration into the head of the organ

The kidneys were slightly enlarged and the cut surfaces yellowish-green Intense green streaking was noted at the apices of the pyramids and the cortices appeared slightly swollen

*Pathologic Examination*—A number of sections for microscopic study were obtained by making longitudinal incisions through the opened common bile duct and included the terminal portion of the latter, the ampulla, and papilla of Vater, the adjacent duodenum and underlying pancreas In the ampulla, the zone of malignant transformation was abrupt, and characterized by enlargement of the acini in its wall with a heaping up of cylindrical and cuboidal cells into multiple layers These acini extended to the surface and were followed by the formation of short, plump, villous projections Approaching the papilla, these villous structures appeared as long, slender, finger-like projections consisting of atypical cuboidal and polyhedral cells scattered irregularly in a fine, fibrillar stroma capped by masses of these cells so that many of them appeared knob-like The tumor cells extended into the muscularis and submucosa of the duodenum, covering the papilla of Vater, the duodenal mucous membrane, however, did not show any involvement in any of the sections examined

The atypical epithelial cells were well differentiated, for the most part, and occurred as cylindrical, columnar or cuboidal elements The nuclei were basally situated in the cells and stained fairly uniformly, only a few showing hyperchromasia Mitotic figures were rarely observed The majority of the tumor cells were arranged in the form of irregular acini lined by a single layer of cells and occasionally by eccentric multiple layers The stroma was generally abundant and not very vascular Many polymorphonuclear leukocytes were irregularly scattered through the mucosa and submucosa of the duodenum covering the papilla of Vater, and they occurred in lesser numbers in the stroma of the neoplastic tissue

The immediately adjacent portion of the pancreas, underlying the ampulla of Vater, showed marked perilobular and interacinar fibrosis with atrophy of the parenchyma and, in one section, three small tumor acini were found extending into the interstices of a pancreatic lobule A large branch of the pancreatic duct appeared dilated but its mucous membrane was normal

The liver showed marked biliary pigmentation, slight degeneration in the inner portion of the lobule and slight fibrosis and moderate bile duct proliferation in the portal radicles. A small metastatic nodule, beneath the capsule of the liver, consisted of irregular, small acini having the characteristics of the primary lesion.

The kidneys showed slight biliary pigmentation and a moderate grade of nephrosis.

**Case 17**—E. F., white female, age 62, was admitted to the Jefferson Hospital, November 14, 1937, complaining of painless jaundice, generalized itching, belching, flatulency, constipation, epigastric soreness and loss of weight. The onset had occurred six months previous to admission. The first complaint had been a substernal sense of suffocation, especially after eating and on effort. Constipation was also noted at this time. About one month later, jaundice appeared associated with generalized itching and clay-colored stools. There was no pain at any time, later, however, she developed a sense of midepigastriaic soreness, especially in the evening. Belching and flatulency had occurred irregularly from the onset. There had been a loss of 27 pounds (12.2 Kg.) during the past six months. Nausea, vomiting, diarrhea and melena were not noted at any time.

*Physical Examination* showed a slight fulness and a definite sense of resistance in the right hypochondrium. The liver edge was sharp, firm, smooth, not tender, and extended four fingers' breadth below the costal margin. The gallbladder was not palpable and no masses could be detected. Roentgenologic studies of the gastro-intestinal tract showed slight broadening of the duodenal curve with delay in the passage of barium through the second and third portions of the duodenum, interpreted as suggestive of some enlargement of the pancreas. Cholecystographic studies showed nonvisualization of the gallbladder. Tests of hepatic function, performed on the second day, resulted in a positive van den Bergh reaction with 10.8 mg. per cent of bilirubin, an icterus index of 61, and a retention of 40 per cent of bromsulfalein in 30 minutes (2 mg. dosage); seven days later, the quantitative van den Bergh test showed 7.44 mg. per cent of bilirubin and 20 per cent retention of bromsulfalein in 30 minutes. *Clinical Diagnosis*: Carcinoma of the head of the pancreas or primary carcinoma of the liver.

*Operation*—November 24, 1937. Dr. George P. Muller. Celiotomy disclosed an enlarged, smooth and jaundiced liver. The gallbladder and common bile duct were markedly dilated. The former was aspirated and its fundus anastomosed to the lesser curvature of the stomach. A curette introduced into the common bile duct met with an obstruction in the region of the papilla of Vater, and a small quantity of soft, friable, gray tissue was withdrawn. The common duct was ligated. The stomach was anastomosed to the jejunum and two loops of jejunum were brought together and anastomosed. *Postoperative Diagnosis*: Carcinoma of the ampulla of Vater. On the second day post-operative, the temperature was normal and the pulse was strong and regular. The intensity of jaundice had diminished somewhat, on the evening of the third day, however, the urinary output decreased markedly, the temperature suddenly rose to 107° F. and death ensued.

*Autopsy*—Nineteen hours after death. Dr. M. M. Lieber. The combined gross and microscopic diagnoses were: (1) Adenocarcinoma, primary in the region of the ampulla of Vater, (2) obstruction of common bile and pancreatic ducts, (3) generalized jaundice, (4) bile pigmentation and acute degeneration of kidneys, (5) acute myocardial degeneration, (6) biliary stasis and necrosis of liver, (7) hypostatic congestion of lungs with left-sided pleural effusion, (8) recent surgical anastomoses of gallbladder to stomach and jejunum, and (9) hemorrhage into the gastro-intestinal tract.

The stomach was markedly distended and contained 600 cc. of bile mixed with blood, the mucous membrane was atrophied. The proximal segment of the duodenum was moderately dilated. The papilla of Vater formed a cylindro-conical body 2.2 cm. long and 1.5 cm. in diameter. The duodenal mucous membrane was smooth and freely movable over all portions of the papilla. The orifice on the apex of the papilla was moderately dilated. On longitudinal section, a gray, soft, friable, granular polypoid lesion 1.5 cm. in length, and completely annular, was disclosed within the papilla. The orifice of the duct

of Wirsung was obscured by the primary growth. In the body of the pancreas, the duct was dilated and measured 4 cm in circumference. Retrograde dissection of the duct of Wirsung showed it to be completely obstructed by the tumor mass in the ampulla of Vater. A number of milium, gray nodules studded the inner lining of the duct near its orifice. The duct of Santorini emptied into the duct of Wirsung, 1.5 cm proximal to the latter's entrance into the ampulla. The common bile duct, proximal to the primary lesion, was moderately distended and its wall hypertrophied.

The liver weighed 1,250 Gm. It cut with slightly increased resistance and the surface was predominately yellow with a slight admixture of green. Small, pin point focal gray areas were scattered through the parenchyma. The larger biliary ducts contained a muddy-yellow fluid while the smaller ducts were dilated and filled with dark green bile.

The pancreas was firm and showed no evidence of extension of the neoplasm into it.

The kidneys were enlarged, bile-stained and showed a marked degree of nephrosis.

The large intestine was widely dilated and filled with liquid and clotted blood.

Microscopically, longitudinal sections taken through the opened papilla of Vater and including the ampulla of Vater, common bile duct and a portion of the underlying pancreas, showed no evidence of neoplastic change in the autolytic duodenal mucosa covering the outer surface of the papilla of Vater. The submucosa was also free of neoplasm except in one small area. The muscular layers of the duodenum were, however, infiltrated with large acinar structures lined by tall cylindrical cells often heaped up to form papillary spurs. The inner surface of the papilla was lined by long, slender, branching processes consisting of narrow cores of fibrillar, vascular connective tissue covered by single or multiple layers of cylindrical cells. In the ampulla, these processes were plumper and shorter and finally appeared as half-moon-shaped nests of flattened cells. In the depths of the tissue, small and large acini were present, the lumina of many of the latter being filled with a homogeneous, eosinophilic substance in which desquamated cells and debris were also present. Similar new formations were also observed in sections of the wall of the duct of Wirsung in its proximal portion. Small acini projected above the adjacent normal mucous surface of the inferior wall of this duct. The underlying pancreatic tissue was separated from the main tumor growth by a band of loose connective tissue which was free of neoplasm. The neoplastic cells were generally well differentiated into tall cylindrical elements with basally situated nuclei showing considerable variation in size, shape and staining; mitotic figures were rarely observed. There was little or no tendency for the cells to grow in the form of clumps, cords or nests. The supporting stroma was scanty, vascular and without appreciable inflammatory cell reaction.

Sections of pancreas showed dilatation of ducts, extensive interlobular and interacinar fibrosis with consequent atrophy of the parenchyma and little or no evidences of inflammation.

The liver showed varying degrees of involvement with necrosis of the inner one-half to two-thirds of the lobules and focal midzonal and biliary necroses. The amount of biliary pigment was small. The characteristic changes associated with decompression of obstructed biliary passages, previously described by us (Stewart and Lieber), were clearly illustrated in this case. These consisted of disruption of intralobular architecture with disorganization and dissociation of hepatic cell cords and atrophy and distortion of the hepatic cells. These changes were particularly pronounced about the larger portal radicles. Hypertrophy, hyperchromasia, binucleation and multinucleation of cells at the peripheries of the lobules indicated regeneration of hepatic cells, but mitotic figures were not observed. There was a marked proliferation of the smaller biliary ducts associated with a pronounced increase in the connective tissue which was periportal, interlobular and perilobular in distribution, and a slight infiltration of lymphocytes and monocytes.

The kidneys contained little or no bile pigment and cortical regressive changes were only moderate in degree.

# NEUROFIBROSARCOMA OF THE SMALL BOWEL

## REPORT OF TWO CASES

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RECOGNITION of neoplasms derived from the nerve trunks is usually credited to von Recklinghausen,<sup>2</sup> in 1882, however, Kolliker, in 1860, and numerous others<sup>1</sup> had described the disease previously. The literature offered covers more than a century and even so, the most recent papers indicate that there still is no uniformity of opinion as to classification and histogenesis. Therefore, any historic review is erroneous, for it is impossible to accept all examples offered as the same type of growth, and many descriptions are not sufficiently clear to permit analysis. It seems quite evident that the fibromata and fibrosarcomata were a composite group which is now being subdivided.

The name, neuroma, is perhaps the oldest one and was used by the writers contemporary with von Recklinghausen, but there are many aliases, each of which was offered as descriptive of structure or specific origin. These include neurilemoma, neuronoma, peripheral fibrogloma, fibroblastoma, neurogenic fibroma, neurinoma, neuroma, peripheral glioma, lemmoma, schwannoma, false neuroma, and perineural fibroblastoma.

These tumors have been found in almost all parts of the body, but they predominate in the skin. It is said<sup>1</sup> they may occur in the digestive tract at any point from the "lips to anus." Many are described in the stomach, a few in the colon, one in the appendix, and a few in the small bowel.

Some of the earliest reports indicate that these tumors in various locations are sometimes malignant. Von Recklinghausen<sup>2</sup> described a malignant one in the jejunum. Adrian,<sup>3</sup> Delageniere,<sup>4</sup> Denecke<sup>5</sup> each reported one in the duodenum. Lemonnier and Peycelon,<sup>6</sup> Dudley,<sup>7</sup> König<sup>8</sup> and Leriche<sup>9</sup> reported one case each, and Noilander<sup>10</sup> describes three cases in the jejunum and ileum. Case reports of neurofibrosarcoma of the small bowel include three in the duodenum and eight in the remaining portion. Most of these were multiple tumors.

*Etiology*—The tumors usually appear during middle age, and they are about equally divided between the sexes.

It is suggested by Masson<sup>11</sup> that trauma or inflammation of the nerve trunks is a possible etiologic factor. He produced tumor growths of nerve trunks in animals by transplanting sections of a peripheral nerve to prevent the axone from coming in contact with the cells of the nerve sheath. It seems the cells of the sheath of Schwann begin to proliferate as soon as degeneration of the axone is well advanced, but this ceases immediately if the regenerating axone enters the sheath. If the neurite is prevented from

entering the sheath, the cells would grow as long as the observations were continued, which was five months. The structure of these proliferating sheaths of Schwann is identical with that of the neurofibroma. However, it is yet to be proved that neoplasia and hyperplasia are identical, in fact, there is much evidence to indicate that continuous growth is a minor or incidental characteristic of neoplasms.

These growths were considered as developmental by Waithin (quoted by Case<sup>12</sup>). This is also suggested by others,<sup>13</sup> who pointed out the association of malformations in some patients with neurofibromata. It seems quite clear that fetal rests may be the origin of neoplastic tissue, but there is very little evidence to indicate that the neoplastic characteristics of tissue are dependent upon faulty development. It is evident that certain carcinogenic agents, the roentgen ray for instance, can bring about neoplastic changes in any or all cells of certain tissues, the squamous epithelium of the skin, for example.

The specific etiology will, therefore, remain obscure until the day when the mechanism of neoplastic development will have been explained.

*Histogenesis*—The structure of the nerve trunk is uniformly described. Briefly, it consists of nerve cell processes, the axones, which may or may not have a myelin coat but are covered by the neurilemma, or sheath of Schwann. These are supported by a delicate framework of connective tissue, the endoneurium. Small groups of nerve fibers with their supporting endoneurium are grouped into strands or funiculi which are surrounded by connective tissue, the perineurium, and these funiculi are also grouped in strands, the nerve trunk, which is supported and surrounded by connective tissue, the epineurium. There are two possible sources, excluding the vessels, of neoplastic growth, the supporting connective tissue and the neurilemma.

Concerning the development of these structures there is also uniform agreement. The connective tissue elements, the epineurium, perineurium, and endoneurium are, like other connective tissue elements, mesodermal in origin. The two remaining elements, the sheath of Schwann, or neurilemma, and the nerve cell processes, are derived from epithelium, the ectoderm, and have a common ancestry in the cells constituting the neural plate. The neurilemma cells grow with the nerve cell processes as they penetrate the tissues during development.

Concerning the histogenesis of neurofibromata there are three points of uniform opinion. First, that neoplasms do develop from the nerve trunk, second, that axones are sometimes found in them, but they are only accidental, and are remnants of the invaded and deranged nerve trunk in which the growth developed, they do not grow, and third, they contain no nerve cells.

Concerning the remaining important point, the mother cells, there is much controversy. It was contended recently by Penfield,<sup>14</sup> and previously by many others,<sup>13</sup> that the parent cells are those of the connective tissue.

elements of the nerve trunks. It would follow that such names as fibroma or perineural fibroblastoma are representative.

It has also been suggested<sup>15</sup> that the tumors are connective tissue but derived from the neurilemma cells by metaplasia. This involves a change from one primary tissue (nerve) to another primary tissue (connective), which perhaps never occurs except in embryonic life and neoplastic development.

Another opinion is that neoplasms do develop from the cells of the neurilemma, and it follows that such names as neurilemoma, peripheral glioma, and schwannoma are correct. This view is supported by Masson<sup>11</sup> and many others,<sup>11</sup> among whom are Vorocay, Pick, and Bielschowsky, who report having seen microscopic neoplasms in which the cells could be traced by continuity to the cells of the neurilemma. Others avoid the controversy by suggesting that any one or both elements of the nerve trunk may be the parent tissue of the neoplasm. And for this interpretation, practically all the evidence presented in argument can be accepted.

The question is not merely academic. Its solution and the specific classification of the growths will quite certainly lead to more accurate prognosis and treatment. In fact, the controversy was initiated by the observation that all fibromata did not behave alike. It seems that the weight of evidence is rapidly accumulating in favor of the theory that the neurilemma is the parent tissue for a rapidly growing list of neoplasms and that the accepted list of pure fibromata is getting smaller and smaller.

*Characteristics*—The malignant growths are like the benign in that they are more often multiple than solitary. The tumor mass is usually spherical or modified spherical, with a connective tissue capsule. If there is no covering, there is a pressure atrophy zone about the mass and diffuse infiltration at the border is lacking. The more malignant ones are soft and friable, somewhat resembling brain tissue. Firmness is increased in proportion to the amount of connective tissue stroma, so that some specimens are hard, but those that are so described are usually benign. The color is gray, and again is similar to that of the brain. Frequently there are yellow areas, necrosis, and black or blood red areas because of hemorrhage. Lobulation is definite except in the most malignant growths. Commonly there are cavities containing grumous material consisting of necrotic tissue and blood, the proportion of blood modifying the color. The wall of the cavity is irregular and friable.

The cells are elongated, stellate, or in localized areas polygonal. Mitotic figures are present and some are atypical. Small giant cells may be present. The cytoplasm stains with eosin but often has a blue quality. There are coarse processes which are blue in phosphotungstic acid hematoxylin preparations. There is a varying amount of fibrillar substance which is collagenous in its behavior to stains. The cells are arranged in interlacing bundles and sometimes in whorls. Palisading is present in some specimens, and if so,

is considered by Masson<sup>11</sup> to be pathognomonic. Often there are imperfectly organized spherical arrangements that are interpreted as aborted attempts at Meissner corpuscle formations. It has been suggested that these formations, the palisades, and the clinical observation that motor paralyses seldom occur, are evidence that the growths have occurred on sensory nerves, that those which do occur on motor nerves have no palisades or imperfect corpuscles. If this reasoning is correct, it may explain the infrequency of neurofibromata in the gastro-intestinal tract, since its sensory nerve supply is meager. The stroma is very small in amount in the malignant ones. The blood vessels are usually numerous, very large, and have thin imperfect walls so that hemorrhage is common and considerable. There may be large blood-filled spaces lined by endothelium supported by only a few connective tissue cells. There is infiltration at the periphery of the growth, but displacement is more prominent. They may be myxomatous. Axones are not found in the malignant tumors.

The grade of malignancy is not high. Stewart and Copeland,<sup>13</sup> in reporting 73 cases, none in the intestine, divided them into Grades I, II and III, placing none of the specimens in Grade IV. There are no reports of grading the intestinal tumors, and the subsequent histories of these reported are too inadequate to be of value.

Metastases are not common but have occurred in the regional lymph nodes, the liver, and the diaphragm.<sup>16</sup> Metastasis to the skeleton has been observed in two instances<sup>17</sup> of malignant peripheral tumors.

Judging from the records, some tumors are malignant at the onset, but von Recklinghausen considered his case as one of a change from benign to malignant because there were other benign tumors in the intestine. Peripheral tumors in which malignant change occurred have been observed.

*Clinical Aspect*—A number of the patients with neurofibrosarcoma of the small bowel have had neurofibromatosis, or von Recklinghausen's disease, for years. In others, there were no peripheral lesions demonstrable. The absence of nerve tumors is difficult to determine, however, since they may be on the deep, large nerve trunks and very small.

The symptoms are usually those of obstruction, either sudden or gradually progressing. Usually the tumor is large enough to be palpated.

*Prognosis*—The group of case reports is too small and incomplete to be of much aid in determining prognosis. The same tumor in other locations has a poor prognosis, the five-year cases reported by Stewart and Copeland<sup>13</sup> being 25 per cent in Grade I, 5½ per cent in Grade II, and 5 per cent in Grade III. If they are multiple, and they are more often than not, resection may be impossible for that reason alone. Since the grade of malignancy is not high, and metastases not common, it seems that resection of the bowel with the tumor would offer a good prognosis if the tumor is solitary.

The first case is that of a solitary lesion springing from the wall of the jejunum opposite the mesenteric attachment.



## CASE REPORTS

**Case 1**—H C, female, age 72, white, married, was admitted to the hospital July 27, 1937, presenting an abdominal tumor. The patient had been apparently well until two years previously, at which time she began to experience a feeling of distress and a sense of fullness low in the abdomen. She developed backache and frequency of urination which during the past six months has been decidedly exaggerated, and within this time she had noticed enlargement of the abdomen. Her past and family histories are entirely negative. She has had eight children, varying in age from 30 to 13. During the past year she had noticed some shortness of breath on exertion and some swelling of the ankles at night.

*Physical Examination*—The patient was somewhat thin but not acutely ill. The head, chest and extremities were entirely negative. There were no nodules either in

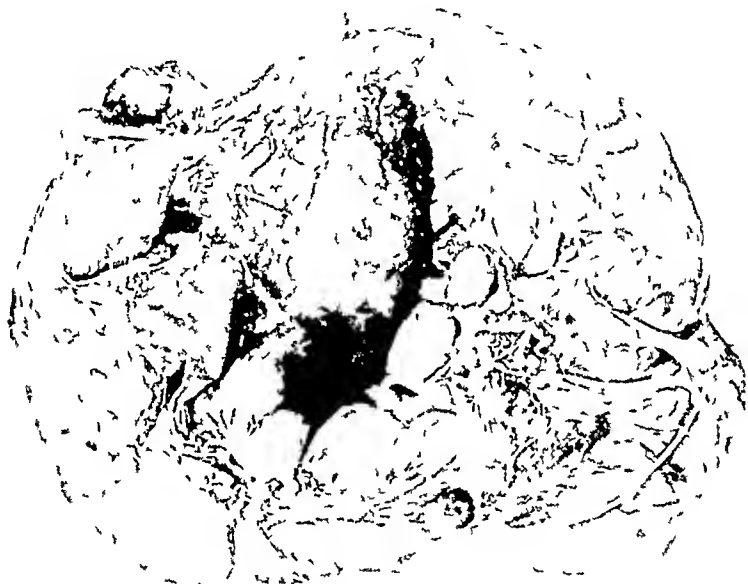


FIG 1—Case 1. Photograph of neoplasm. The small pedicle of attachment is at the lower left and the adherent omentum at the lower right. The large cavity was filled with necrotic tumor tissue and blood.

the arms or legs or any areas of pigmentation. Blood pressure 200/110. There was a distinct fullness in the lower abdomen extending mostly to the right side. Over this area there was dullness to percussion. This fullness or mass extended from the symphysis to about one and one-half inches above the umbilicus; it was soft and apparently fluctuant. The flanks were tympanitic. The upper abdomen was soft, relaxed and contained no masses. The liver was not enlarged nor was the spleen palpable. Pelvic examination revealed a relaxed perineum, normal cervix, and a tumor mass which filled the culdesac and was apparently continuous with the mass in the abdomen, extending up to about one and one-half inches above the umbilicus. Definite fluctuation could be obtained.

Urinalysis was negative other than for a trace of albumin. RBC 3,620,000, Hb 74.6 per cent, WBC 10,350, with 92 per cent neutrophils, 1 per cent monocytes and 7 per cent lymphocytes. Kahn and Wassermann tests were negative. *Preoperative Diagnosis*: Right ovarian cyst.

*Operation*—On opening the abdomen, a mass presented which extended from the pelvis almost to the costal margin. The left side of the mass seemed cystic and had the appearance of a gangrenous cyst wall such as is seen in twisted ovarian cysts. On the right side, however, this cyst was apparently continuous with some tissue which had the

appearance of brain. While separating the adhesions between this tumor and the pelvic organs, a gush of old blood together with some necrotic tissue resembling broken-down carcinoma, was encountered. It was found that there was no attachment of this tumor to the pelvic organs except by very fine, fresh adhesions which were easily separated without bleeding. The omentum was adherent to the upper part of the tumor and was divided between ligatures. It was then found that the tumor was densely adherent to, or sprang from, a loop of jejunum in the upper left abdomen. It being impossible to separate the mass from this piece of intestine, a clamp was placed about the pedicle in the long axis of the bowel, and the tumor, together with the wall of the jejunum, was cut away. The opening in the jejunum was then closed and inverted with linen sutures.

A thorough inspection of the abdomen revealed that there had been some adhesions between the tumor and the peritoneum of the right lateral wall of the abdomen at about the level of the anterior-superior spine. Furthermore, there had been some adhesion to



FIG 2.—Case 1. Photograph of opposite side of attachment of tumor mass. There are deep fissures dividing the tumor into irregular lobules. The color is light gray, consistency soft.

the peritoneum above the bladder. Otherwise, the tumor was apparently free except for its attachment to the omentum and to the jejunum. The pelvic organs were normal. There were no nodes in the mesentery of the jejunum. The liver was of normal size, soft, and contained no metastatic nodules nor were any nodules evident in the spleen. The gallbladder contained no stones, the stomach was normal.

*Pathologic Examination—Gross.* The specimen is a neoplasm in the shape of a flattened sphere and measures 28 cm in greatest diameter. It has a small area of attachment, evidently by a pedicle, about 2.4 cm. Near this a small portion of the great omentum is adherent. The surface covering is thin peritoneum in which there are many large vessels. The contour is marked into irregular lobule formations by wide, shallow fissures. The mass has been opened near the pedicle and the content, which was necrotic tumor tissue and blood, has escaped, leaving a shell 1 to 3 cm in thickness. The tissue is very friable, grayish substance without striations (Figs 1 and 2).

*Microscopically,* sections show very dense parenchyma with almost imperceptible stroma. The cells are arranged in bundles that extend in all directions, and also in whorls. The cytoplasm is moderately abundant and extends in wide and coarse prolongations. There is a small amount of fibrillar intercellular substance. The nuclei have large chromatin granules, large true and false nucleoli, and a few are vesicular. There

is an occasional mitosis. Phosphotungstic acid stains reveal no glia. The stroma is very delicate reticulum bearing blood vessels with only a lining of endothelium and a thin layer of connective tissue cells (Figs 3 and 4). The arrangement of the cells and their staining reaction suggests a neoplasm of the nerve sheath origin. *Pathologic Diagnosis*—Neurofibrosarcoma of small bowel.

FIG 3

FIG 4

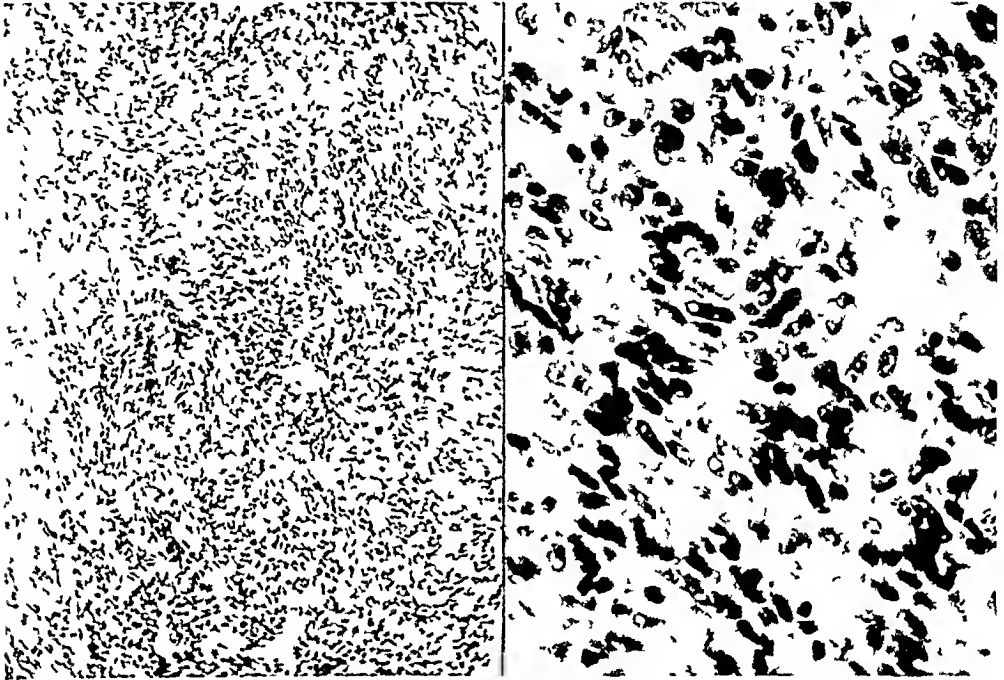


FIG 3—Case 1. Photomicrograph showing many bundles of fibers extending in various directions and imperfect palisading. There are numerous blood sinuses. (Low power.)

FIG 4—Photomicrograph showing the cells arranged in definite palisades. (High power.)

The patient made an uneventful recovery, temperature never going above 99° F, and she was dismissed from the hospital on the tenth postoperative day, with the advice that she return in four weeks for roentgenotherapy. Six months after operation she was without complaint.

The second case is interesting from the fact that the smaller as well as the larger lesions all present the same picture.

**Case 2**—I. B., male, age 47, had consulted a physician on account of loss of weight and was thought to have tuberculosis. He complained only of weakness, loss of weight and vague abdominal discomfort occasionally associated with griping pains.

Physical examination was entirely negative other than for slight tenderness to deep pressure over the left lower quadrant. Roentgenologic examination was negative for tuberculosis. A thorough gastro-intestinal study not only of the stomach and colon, but hourly examinations of the small intestines failed to reveal any abnormalities.

Urinalysis was negative. R B C 3,980,000, hemoglobin 73.3 per cent, W B C 11,150, 77 per cent neutrophils, 14 per cent lymphocytes and 9 per cent monocytes. *Preoperative Diagnosis*—Intra-abdominal malignancy, source unknown.

*Operation*—February 15, 1933. Exploration of the abdomen revealed the liver and spleen to be normal. There was no evidence of any carcinoma in the stomach or duodenum. Beneath the ligament of Treitz was a mass about the size of an orange, which had grossly the appearance of ovarian tissue. It was grayish-white in color and extended

up toward the left kidney, but the kidney itself did not appear to be the source of the growth. The right kidney was normal. There were no tumors in any part of the colon. The prostate was apparently normal. No implants of neoplastic tissue were evident in the culdesae. Beginning at the ligament of Treitz and extending throughout the length of the small intestine down to the ileocecal valve were many tumors varying in size. All the lesions except the very largest presented the same characteristics. The largest ones grew outward on the bowel wall, were of a yellow color and apparently were not obstructing the lumen of the intestine. The smallest ones were of a yellowish color, slightly umbilicated, and seemed to spring from the intestine beneath the serosa. In many places, where these tumors were 1 cm or more in diameter, there was partial intussusception. In none of these was the intussusception of greater length than 2 cm and all were easily reducible.

It being utterly impossible to remove all of the neoplastic tissue, a resection of approximately 16 inches of the ileum was performed for biopsy purposes.



FIG 5—Photograph of section of jejunum with tumors. The ends of the specimen are opened to show the ulceration and the protrusion of the tumors into the bowel lumen causing obstruction.

*Pathologic Examination—Gross.* The specimen consists of 38 cm of the jejunum (Fig 5). There are five tumor masses in the wall of the bowel, one large one near each end. They are from 0.5 to 4.0 cm in diameter on the surface and from 0.25 to 2.50 cm in thickness. All produce some obstruction but the largest one closes the lumen, except for a small opening about 1 cm in diameter, by protruding into it. They are all covered by serosa, some of them rounded and others puckered and depressed. The mucosa opposite the depressions is ulcerated, but over two of them it is intact. The sectioned surface reveals grayish, very friable neoplastic tissue that is quite vascular and contains numerous small, recent hemorrhages. The margins of the ulcers overhang somewhat, but the lining is not thickened and there is no suggestion of continuity of tumor tissue and mucosa. The margins are infiltrating and the bowel wall destroyed. The main mass of tumor tissue is sometimes internal and sometimes external to the muscle coat.

*Microscopically,* sections show a neoplasm, made up of a very cellular parenchyma and an inconspicuous, delicate stroma. The cells are arranged in irregular bundles, extending in all directions, and also in imperfect whorls. They are elongated and stellate-shaped with a moderate amount of cytoplasm which is extended into short coarse processes. There is a small amount of fibrillar, intercellular substance. The nuclei are dense with chromatin, but in some cells it is arranged in large granules and there are large nucleoli (Figs 6 and 7). A few cells show mitosis. Blood vessels are numerous and thin-walled.

The tumor is malignant. Its origin from the nerve sheath is suggested by the

irregular bundles and imperfect whorls of fibers together with the general character of the cells. Whether they are metastatic or multicentric growths cannot be determined with certainty, but since multiple origin is common in this type of neoplasm this interpretation is first choice. *Pathologic Diagnosis* Neurofibrosarcoma, multiple, of jejunum, with partial obstruction.

Convalescence was uneventful, and the patient was discharged on the fourteenth day postoperative. Death occurred three months later, May 16, 1933. An autopsy was obtained.

*Autopsy*—External examination reveals a markedly emaciated white male. The abdomen is moderately distended, in the midline is a well-healed surgical scar. Incision is made in the abdomen only.



FIG. 6—Photomicrograph showing the tumor invading the submucosa of the ileum (M) Mucosa (T) Tumor. The cells are arranged in interlacing bundles and there is imperfect palisading. (Low power.)

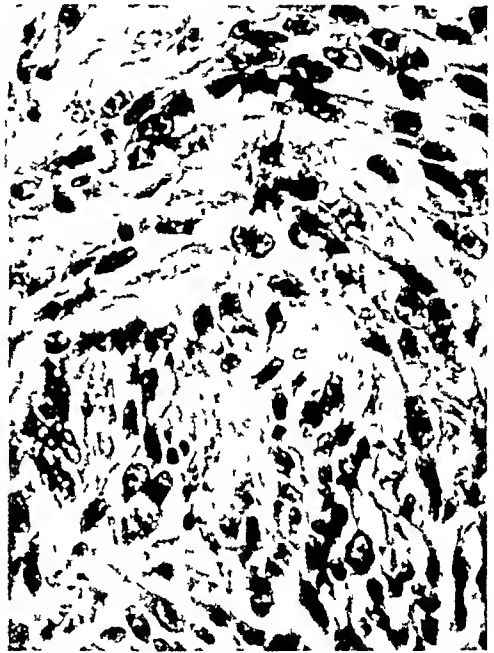


FIG. 7—Photomicrograph showing two large strands, one curved around the other. Cell outlines are indistinct and morphology moderately irregular. Some cells have coarse fibrils. (High power.)

The peritoneal cavity contains about 1,200 cc of blood tinged fluid. The thoracic cavities are free from fluid and adhesions. No chriages are noted in the gastro-intestinal tract except for the small bowel. It is moderately distended with gas, and the site of the resection is adherent to the parietes anteriorly. At various intervals there are spherical tumors measuring from 1 to 10 cm in diameter. They are covered by serosa. Some of them are annular with large lumina formed by the necrosis of the inner surfaces (Fig. 8). Many of them form partial obstruction by protrusion into the bowel. Section reveals friable, grayish neoplastic tissue, the central part of which is necrotic, and here and there are old and recent hemorrhages. Some of the inner surfaces are ulcerated, others covered by mucosa. The gross appearance is identical with that of the surgical specimen. In all, 21 tumors are counted in the bowel wall, and there are eight or more in the mesentery and retroperitoneal lymph nodes in the upper half of the abdomen, none are found in the pelvis or at the bifurcation of the aorta. One is found beneath the peritoneum and in front of the left kidney, but the kidney is not invaded.

There are no tumors in the lymph nodes of the thorax or in the viscera of the chest and abdomen, including the adrenals, or in the prostate and testes. There is very early

bronchopneumonia in the posterior aspect of each lung. The liver is small and dark from starvation, and all the viscera are soft from cloudy swelling.

Microscopy reveals a neoplasm identical in structure with that of the surgical specimen, and early bronchopneumonia.

*Comment.* It does not seem probable that the tumors have arisen from a postperitoneal focus, although a spread by way of the superior mesenteric artery would explain their location except for the one anterior to the kidney, and if this had happened the colon could have received metastases. The location of some of the masses will admit the possibility of a primary focus in one of the semilunar ganglia or others of



FIG. 8.—Photograph of the distal two-thirds of the small bowel and part of its mesentery. There are numerous enlargements caused by tumor growth in the wall. The largest one (T) is a truncated tumor replacing the bowel with a lumen through it. There are also masses in the mesentery.

the sympathetics and, if so, the ganglion was completely destroyed. The largest tumors are in the bowel wall, however, and phosphotungstic acid stains reveal no glia fibers. Nerve sheath tumors are commonly multicentric, although there are no definite criteria by which it can be determined which of these tumors arose by metastasis or by neoplasia.

*Postmortem Findings.*—Neurofibrosarcoma of small intestine, metastasis to mesenteric and postperitoneal lymph nodes, other postperitoneal metastases, emaciation, early bronchopneumonia.

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# DILATATION OF THE COLON<sup>\*</sup>

REPORT OF A CASE FOLLOWING THE DEVELOPMENT OF AN AORTIC ANEURYSM,  
RELIEVED BY DILATATION OF THE ANAL SPHINCTERS

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MEGACOLON, or better termed dilatation of the colon, may be classified into two types: Congenital or idiopathic, and acquired or secondary. The former is not caused by any organic obstruction and is present at birth or evidenced by signs and symptoms in early childhood. The latter may appear in childhood, but occurs more commonly later in life, and is secondary to a gradually increasing partial obstruction of the rectum or sigmoid. The cases of the idiopathic type, when first recognized in late childhood or later in life, can be traced back to early childhood, by a long history of a distended abdomen and obstipation, characterized by bowel movements at intervals which may vary from three days to several weeks.

**Case Report**—Hosp. No. 96215, F. V., white, male, age 73, was admitted to the Medical Service, St. Luke's Hospital, New York, August 3, 1937, complaining of increasing swelling of the abdomen during the preceding two months, associated with obstipation which had become so complete that he had had no bowel movement for several days preceding his admission. During the two months of his present illness he had lost 20 pounds in weight. In addition to the acute condition, he gave a history of having had a moderate degree of constipation for many years, but one which had been in no way remarkable, having been readily controlled by the use of mineral oil and enemata.

In 1932, at the age of 68, he had been operated upon at St. Luke's Hospital, for an acutely thrombosed hemorrhoid, which was excised, with complete relief. At that time, his physical examination was otherwise negative, and the abdomen was described as being flat and flabby, without distention. In 1935, he returned to the Medical Clinic because of fatigue. Slight widening of the aortic arch and moderate enlargement of the heart were found. The abdomen was described as entirely negative. The blood Wassermann reaction was negative. At intervals during the next two years, he was seen in the Medical Clinic and treated as a cardiac case. A gradual increase in the width of the aorta was noted, eventually, a definite aneurysm of the descending aorta presented. The abdomen was not found distended at any of the examinations in the clinic.

**Physical Examination**—The patient appeared chronically ill. Percussion revealed an aneurysm of the aortic arch and the descending aorta (Fig. 1). At both bases were a few moist rales. The abdomen was enormously distended, tense and tympanic. Rectal examination was negative except that the sphincter was about the size and shape of a closed fist. It was very tense and spastic, but there was no stricture in the muscle or the areas about it, only a condition of firm contraction in a greatly hypertrophied sphincter. Proctoscopic and sigmoidoscopic examinations were negative.

Neurologic examination revealed the deep reflexes absent throughout with the excep-

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<sup>\*</sup> Presented before the Surgical Section of the New York Academy of Medicine, December 3, 1937. Submitted for publication January 11, 1938.



tion of the left knee jerk, which was obtained with reinforcement. The abdominal reflex on the left was greater than the right. Vibratory sensation was decreased in the feet. The gait was unsteady with the eyes closed. The fundi showed marked arteriosclerosis. The pupils were unequal and small but reacted to light and accommodation. *Neurologic Diagnosis:* Subacute combined sclerosis, arteriosclerotic degeneration of the cord.

An electrocardiogram, August 4, 1937, showed normal rhythm, left preponderance, inverted T-wave in Lead I—evidence of myocardial damage. Another, on August 18, was the same with the exception that Lead II also presented an inverted T-wave.

When roentgenograms were made following barium installation into the colon, the

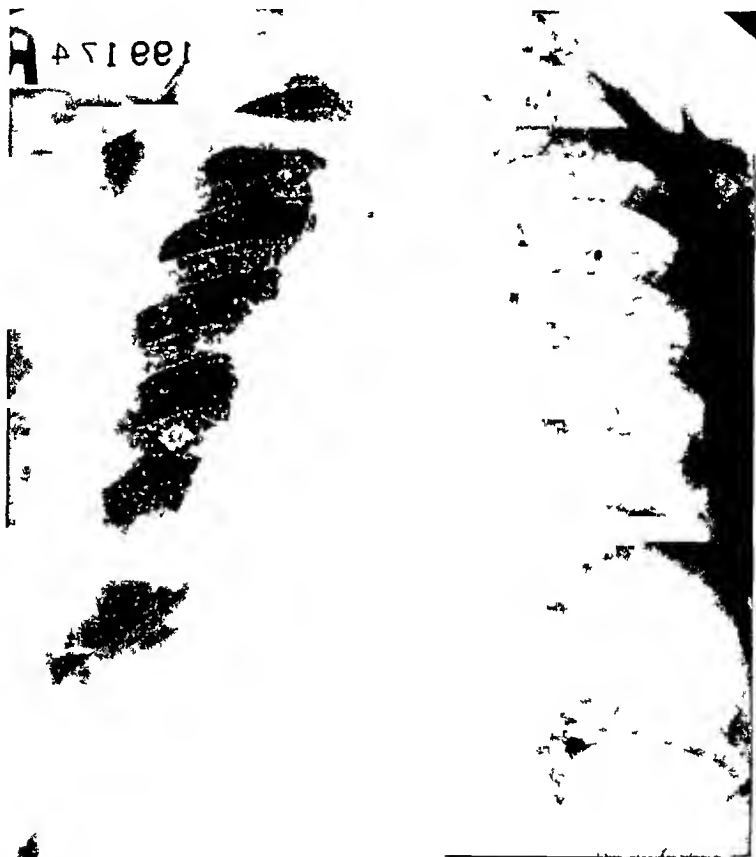


FIG 1—Roentgenogram of the chest made on July 30, 1937. The aneurysm of the aortic arch and the descending aorta can be seen. The trachea is deviated to the right. There is moderate enlargement of the heart. The distended colon can be seen pushing both sides of the diaphragm upward.

abdomen was found to be so enormous that it was necessary to film it in sections (Figs 2, 3 and 4). The barium could be forced only into the transverse colon because of the size of the large intestine and the large amount of gas and fluid which it contained. The clysma revealed an enormous dilatation of the entire large bowel. Those portions not outlined by barium were readily seen due to their distention with gas.

A regimen of enemata and colon irrigations gave practically no relief. Because of the patient's poor physical condition, resection of the presacral nerve was considered to be contraindicated.

*Procedure*—August 25, 1937 (after three weeks of unsuccessful medical treatment). Under gas-oxygen anesthesia, the anal sphincters were slowly dilated until the whole hand could be introduced into the rectum. For several days following this treatment there

## DILATATION OF THE COLON

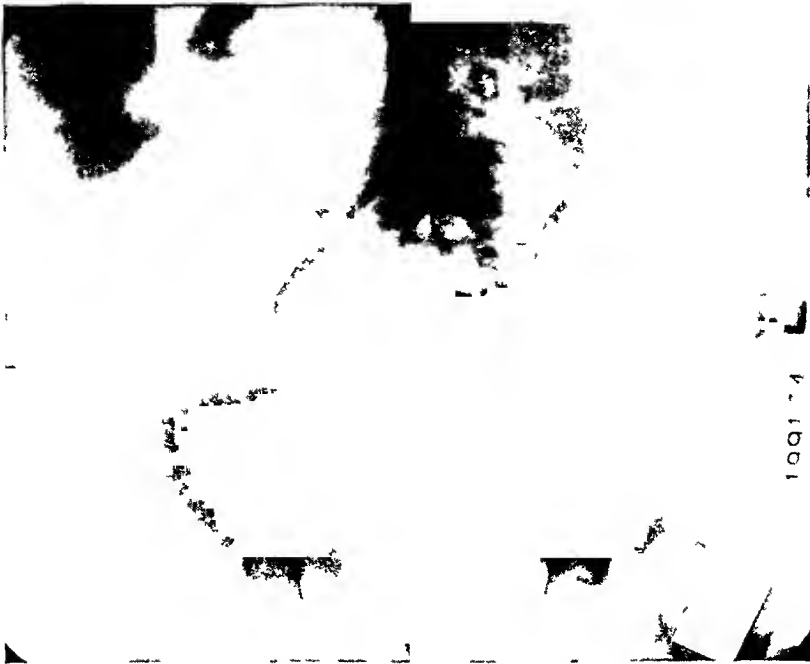


FIG 2—Roentgenogram of a clyisma taken on August 4, 1937. The rectum, sigmoid and lower part of the descending colon can be seen to contain barium. The outline of the cecum, part of the ascending colon, and a loop of the transverse colon are shown outlined by their contained gas.



FIG 3—Roentgenogram taken somewhat higher than that shown in Fig 2 and after more barium had been allowed to run into the colon. The size of the sigmoid is better shown. Some barium has now reached the ascending colon although the cecum contains only gas and non opaque fluid.

was nearly complete rectal incontinence, which then gradually disappeared. He was given daily colon irrigations with excellent results. Large quantities of liquid feces passed from the rectum almost continuously. His abdomen rapidly became smaller.

On September 3, 1937 (nine days after the dilatation), the abdomen had returned to normal size, a reduction of 19 inches in diameter. The bowel movements were under good control. Palpation of the abdomen now that it was deflated, revealed no aneurysm of the abdominal aorta or other masses. A barium clisma showed the large bowel greatly diminished in diameter (Fig 5). He was discharged September 8, 1937, symptomatically, completely cured and with the contour of his abdomen normal.

Eight months after discharge, his physical condition had become markedly improved and he had gained about 15 pounds in weight. His blood Wassermann reaction was again negative. Blood count: Hb 72 per cent, RBC 4,100,000, WBC 7,200, polymorphonu-



FIG. 4—Roentgenogram of the upper part of the abdomen. The barium has reached the splenic flexure. There is also a small amount in the ascending colon. The distended loops of the transverse colon can also be seen. Note that in the three roentgenograms of the clisma the lateral extent of the ascending and descending colon is beyond the edges of the films which are 16½ inches wide.

clears 70 per cent, lymphocytes 23 per cent, mononuclears 1 per cent, eosinophils 5 per cent and basophils 1 per cent. The neurologic examination was unchanged.

When last seen, nine months after the dilatation, the bowel movements were well controlled by the use of mineral oil, dietary regimen and enemas. The contour of the abdomen had remained normal. He had maintained his gain in weight and his general physical condition was somewhat improved.

*Discussion*—After a brief search of the literature no reference could be found of dilatation of the colon following the development of an aortic aneurysm or associated with a subacute combined sclerosis, nor was any reference found to the procedure of dilatation of the anal sphincters as a treatment for the idiopathic type of dilatation of the colon. Two articles<sup>1 2</sup> did, however, report six cases successfully treated by partial sphincterectomy. At present, children with idiopathic dilatation of the colon are being treated,

## DILATATION OF THE COLON

apparently successfully, by the use of syntropan and, thereby, avoiding resection of the presacral nerve

The case which is reported herewith is unique in a number of respects. Insofar as it is possible to tell, the dilatation of the colon was not congenital, nor was it caused by any organic obstruction, as is ordinarily the case when this condition is of the acquired type. It appeared late in life (age 73)



FIG 5—Roentgenogram of a clyster taken on September 3, 1937, which was 9 days after the dilatation of the sphincters. The decrease in the size of the colon is readily noted. The barium has reached the distal part of the transverse colon. The more proximal portions of the colon are seen to contain gas but are less in diameter than in the roentgenograms made before the dilatation. The abdomen had decreased 19 inches in diameter in the interval.

following the development of an aortic aneurysm and a subacute combined sclerosis due to arteriosclerotic degeneration of the cord. Whether or not either of these conditions was an etiologic factor, by causing an imbalance of nerve impulses to the sphincters and possibly to the colon, one cannot say. This possibility must, however, be considered.

The result obtained by thorough dilatation of the anal sphincters was much better than had been hoped for at the time it was employed as a form of treatment in this case, in that the relief obtained was complete and to

date (after a period of over nine months) that relief has continued. Of course, only time will tell whether or not this relief will be permanent. The expectation is that in all probability it will be only temporary. However, he will stand successive dilatations, should the necessity arise, much better than an extirpation of the presacral nerve.

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# CELIAC GANGLIONECTOMY AND PLEXUS RESECTION FOR TABETIC GASTRIC CRISES

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TABETIC gastric crises which do not react to conservative medical treatment have stimulated the performance of a variety of surgical procedures, with indifferent results. The author desires to report a case of gastric crises satisfactorily treated by excision of the celiac ganglia and plexus and periarterial sympathectomy of the celiac axis and branches, following successful preoperative diagnostic novocain block.

The typical gastric crisis is characterized by severe abdominal pain and vomiting. It is generally understood that pain originating in the stomach travels over sympathetic pathways to the celiac plexus and ganglia and then, solely, over the splanchnic nerves. Vomiting is a reflex reaction. The afferent component may be mediated through vagal fibers in the stomach, sensory nerves, or other afferent nerves, irrespective of their origin, they reach the medulla. The efferent impulses producing tonic contraction of the pylorus and antrum are transmitted over the vagus, those inhibiting the fundus and relaxing the cardia are transmitted over the splanchnic nerves.

The celiac plexus and ganglia have important anatomic connections with the vagi. Gastric fibers of vagal origin travel into and through these structures, some coursing, in company with sympathetic fibers, in the left gastric, splenic, and hepatic periarterial plexuses. Splanchnicectomy alone would not affect these vagal fibers, whereas extirpation of the celiac ganglia and plexus, and periarterial sympathectomy of the branches of the celiac axis would have the obvious advantage of a combined sympathetic and vagal interruption. The author knows of no previous case in which this method of treatment has been employed for the control of tabetic gastric crisis.

**Case Report**—Service of Dr Harold Brunn S J, male, age 46, complained of severe gastric crises of tabetic origin. He had a constant burning sensation over the epigastrium. At the onset of a crisis this burning became aggravated after a meal, changed to a sharp pain and radiated to the back. This was followed by nausea and finally vomiting with marked retching. On several occasions he vomited blood. Since their onset, in 1913, these crises had occurred in rapid succession, with intervals of respite between attacks of only one or two days, except for a period of three weeks in 1919. During the past few years they have become more severe and of longer duration, lasting, at times, as long as ten days, and consisting of constant pain and vomiting. In the interval between attacks, belching was a frequent and annoying symptom.

At the age of 16, he had a pemle lesion without secondaries. In 1913, his blood Wassermann was found to be 2+. He had urinary retention. Antiluetic treatment was instituted and since then his blood Wassermann and Kahn have been negative on five

occasions and his spinal fluid has been normal on three occasions, the last time in October, 1936. He had vigorous antiluetic therapy since 1919, when the diagnosis of tabes was first made. He had three pyiotherapy treatments in 1924. The following objective findings substantiated the diagnosis: (1) Pupils asymmetrical, reaction to light markedly impaired on both sides, especially on the right, reaction to accommodation impaired, (2) slight atrophy of both optic disks, (3) absent patellar and Achilles reflexes, (4) Romberg positive, (5) bands of disturbed sensation in the lower dorsal and lumbar distribution, and (6) bladder retention. Drs. Leroy Biggs and M. R. Hirschfeld concurred in the diagnosis of tabes dorsalis. Gastro-intestinal roentgenograms were negative on three occasions.

During the entire course of his illness the picture was obscured by a marked radiculitis involving the roots from the sixth dorsal to the fourth lumbar but most often from the tenth dorsal to the fourth lumbar with varying anesthesia, hypesthesia, hyperesthesia, and paresthesia in the areas of distribution. In addition, there were complicating symptoms of a widespread hypertrophic arthritis of the thoracic spine. In May, 1935, 1 cc of absolute alcohol was injected into the lumbar subarachnoid space in the hope of relieving lightning pains in the lower extremities, with a satisfactory result. In April, 1936, he was fitted with a brace which immobilized his thoracic spine with considerable relief.

Despite all efforts the crises progressed. The patient was seen by the author, June 9, 1935, during an unusually severe crisis which had already persisted for three days. He had only slight and transient relief from two hypodermics of morphine sulfate and was in a state of collapse. The region in front of the first and second lumbar vertebrae was then suffused with 20 cc of 1 per cent novocain injected on each side according to the method of Labat for splanchnic block. In 15 minutes there was a spectacular relief of both pain and vomiting.

In view of the failure of medical management, the increasing severity and duration of the crises, and encouraged by the successful result of diagnostic novocain block of the celiac plexus and ganglia, surgical removal of these structures was offered to the patient with no guarantee as to the result. Before operation, tests were made to act as a basis of comparison for any possible effect of the operation on organs supplied by the celiac plexus and ganglia.

*Operation*—October 10, 1936. The abdomen was opened through a left upper paramedian incision. There was no evidence of organic disease of the stomach, duodenum, kidneys, pancreas, liver, or small intestine. The stomach was drawn caudad and a vertical rent made in the gastrohepatic omentum directly in the midline. The pancreas was drawn gently crudad, exposing the celiac axis. The celiac plexus was excised as completely as possible. The anterior surface of the aorta was denuded of sympathetic fibers in this region. It was, of course, impossible to resect all the sympathetic fibers in this area. The dissection was made unusually difficult by the presence of a number of large veins and venous plexuses. A periaarterial sympathectomy was then performed on the celiac axis and its branches. The left gastric artery was cut between ligatures of silk. The splenic artery was denuded of all its adventitia for a distance of one inch from its origin. In the dissection it was injured and was ligated. The hepatic artery was successfully denuded for a distance of one inch from its origin. There was a heavy layer of interlacing sympathetic fibers on these vessels. After the adventitia had been removed, the diameter of the artery was reduced almost one-half. The splanchnic nerves were then cut close to their attachments to the celiac and aorticorenal ganglia. The suprarenal glands were exposed separately, and the wide band of fibers connecting the celiac ganglia and plexus to the suprarenal glands was sectioned on each side close to the suprarenal glands. The celiac and aorticorenal ganglia were then removed. The rent in the gastrohepatic omentum was approximated and the abdominal cavity closed in layers. The post-operative course was uneventful.

*Subsequent Course*—Since operation there has been a great improvement in his gastric symptoms. He had only six very mild and short attacks of nausea and vomiting.

CELIAC GANGLIONECTOMY

These occurred following unusually severe root pains in the legs and groin, or psychic upsets. Except for these attacks, he has been free of gastric symptoms, and the improvement has persisted until the present, 26 months after operation. He has a good appetite and eats and drinks everything, including alcohol and the foods he previously could not tolerate.

TABLE I  
LABORATORY DATA

	Preoperative				2 Wks Postoper				3½ Mos Postoper				Almost 1 Yr Postoper			
Blood Chemistry																
Amylase	4 units				3				4 6				7 5			
N P N	34 mg per 100 cc				25				28 3				27 3			
Cholesterol	178 mg per 100 cc				190				157				178 5			
Chlorides	445 mg per 100 cc				495				448				420			
Glucose Tolerance Tests																
	Blood Sugar		Urine Sugar		Blood Sugar		Urine Sugar		Blood Sugar		Urine Sugar		Blood Sugar		Urine Sugar	
Fasting	60 mg per 100 cc		0		65		0		62		0		64 5		0	
½ hr	111 mg per 100 cc		0		142		0		181		0		100 0		—	
1 hr	121 mg per 100 cc		0		133		0		167		0		142 8		—	
2 hrs	80 mg per 100 cc		0		60		0		64		0		62 0		0	
Gastric Analyses																
	Fast	1	2	3	Fast	1	2	3	Fast	1	2	3	Fast	1	2	3
Volume	9	5	4	7	14	10	5	12	13	12	16	29				
Mucus	x	x	x	x	x	x	x	x	x	x	x	x				
Free HCl	14	6	7	13	30	7	20	32	11	8	16	38	20	8	12	11
Total HCl	25	14	15	34	46	11	40	40	39	26	34	48	50	34	38	26
Bile Pig	0	0	0	0	x	x	x	x	x	x	x	x	0	0	0	0
Blood (occult)					x	x	x	x	x	x	x	x				
Blood (gross)					0	0	0	0	0	0	0	x				

Kidney Function Studies

Intramuscular Phenosulphonphthalein														
1st hr		40%							35%				5%	
2nd hr		5%							30%				15%	
Addis' conc count	Within normal limits				Within normal limits									

Laboratory studies were made before operation and on three occasions after operation (Table I). There was no evidence of significant postoperative change in the blood nonprotein nitrogen, amylase, cholesterol, chlorides, or sugar, no abnormal variation in glucose tolerance test, phenosulphonphthalein excretion test, Addis' kidney concentration test, or uranalysis, and normal levels in gastric free and total acidity. Likewise, Brown<sup>2</sup>



found no demonstrable changes in the gastric acidity of three cats treated by bilateral coeliac ganglionectomy. The tests did not confirm in humans the increased glucose tolerance reported by DeTakats and Cuthbert<sup>3</sup> in dogs similarly treated. The clinical course gave no evidence of disturbed function of the kidneys, pancreas, or stomach. Before operation his blood pressure varied between 130/80 and 140/80, after operation between 100/66 and 140/90.

These results are not indicative of the effect of such an operation in cases of diabetes or hypertension. The operation is one directed toward alteration of function, and the results upon normally functioning organs are not the gauge of its possible effect on dysfunctioning organs. One may conclude that removal of the human coeliac ganglia and plexus is not followed by any disturbance of function in organs supplied by it, insofar as one is able to judge by the tests reported herein or in the clinical course of the patient.

#### SUMMARY AND CONCLUSIONS

A case is reported of intractable gastric crises of tabetic origin relieved following surgical excision of the coeliac plexus and ganglia. The site of surgical attack was determined by a successful preoperative diagnostic novocain block of the region in front of the first and second lumbar vertebrae. The improvement has persisted until date 26 months after operation. Preoperative and postoperative laboratory studies show no significant changes in the function of the stomach, pancreas, or kidneys, and no abnormal alteration of blood chemistry. The operation had no apparent ill effects, as indicated by laboratory studies or clinical course.

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# BILATERAL AND UNILATERAL RENAL AGENESIS

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CONGENITAL abnormalities of the upper urinary tract have been reported much more frequently in recent years due to the increased interest and investigations of both the urologist and pathologist. We are concerned here with the postmortem findings of 12 cases of renal anomalies of which two were bilateral absence of kidneys, and ten were congenital solitary kidneys.

*Bilateral Renal Agenesis*—Bilateral metanephric agenesis is a rare anomaly, and is a condition incompatible with extra-uterine life. The fetus is frequently alive at birth, but death occurs in a few hours. This condition is usually associated with other equally serious defects of development. In a very thorough review of the literature, Amolsch<sup>1</sup> reported 119 cases, including four of his own, which with the two cases herewith reported, totals 121 cases of bilateral renal agenesis. These were the only two instances of complete absence of both kidneys found in over 12,000 autopsies performed at Cook County Hospital since 1929.

## CASE REPORTS

**Case 1**—Anna B. was born at full term and lived 18 minutes.

*Postmortem Examination* revealed a cyanotic, white female infant, weighing two and one-half pounds, and measuring 33 cm. total length with umbilical cord attached. The head is much flattened from side-to-side, and blood exudes from the nose. No mention was made of the internal organs. The kidneys, ureters, and renal arteries cannot be found. The external genitalia are normal appearing. The opening of the urethra is wide, and located 1 cm. from the region of the clitoris. It is normal and located on the anterior vaginal wall. Its circumference is 7 mm., and it leads into a much narrowed tube-like bladder which is 25 mm. long and 3 mm. in diameter. From the upper end of the bladder, an obliterated cord-like urachus, 17 mm. long and 2 mm. in diameter, extends up to the umbilicus and is accompanied by the umbilical arteries which are patent. No ureteral openings (orifices) can be found in the bladder. Beyond the urethral opening, the vagina extends only as a small pocket 1 mm. in diameter and 3 mm. long. No uterus, fallopian tubes or ovaries can be definitely made out, and no culdesac is present. Lying on the serosa of the posterior lumbar muscles on both sides there are elongated, light pinkish-yellow structures. The left one is 30x3x1 mm. The right is 32x2x1 mm. From the lower ends very fine cord-like structures extend downward. On the left side this structure ends behind the upper end of the bladder. On the right side it seems to disappear into the fascia along the external iliac artery.

*Microscopically*, the flat bodies in the lumbar region are found to be ovaries, in which numerous well developed primordial follicles are present and imbedded in a cellular stroma with ill defined cords of cuboidal cells. The cords extending from these bodies to the bladder consist only of connective and fat tissue and blood vessels. A transverse section taken through the bladder and rectum in the region normally occupied by the uterus shows bladder and rectum connected by loose vascular connective tissue in which there is

no indication of a uterine anlage. The same holds true of a vertical section made through this region. The adrenals were not recorded.

**Case 2**—Paul M. was born at seven and one-half months, and lived three hours.

*Postmortem Examination* revealed a white, male infant, weighing 2,060 Gm. that measured 40 cm. total length. The essential findings were the absence of both kidneys and ureters, the renal arteries were very narrow as was also the right renal vein, the bladder was small and contracted, ureteral orifices were not found, penis and testes were normal. The adrenals were not recorded.

*Etiology*—No single factor can fully explain all recorded cases of renal agenesis. They are always accompanied by some evidence of maldevelopment in distant and not closely related organs. The most popular etiologic concept is that of abnormal pressure exerted during embryonic development by inflammation, or by decrease or absence of amniotic fluid, or by amniotic adhesions. It is true that in some cases pressure by any of the above factors on the caudal myotomes may stunt the growth of the caudal end of the wolffian duct and result in renal agenesis. But this is true of only a small percentage of cases. Rainer<sup>2</sup> believes that the differentiation of the nephrogenic cap is dependent upon the stimulus evoked by the growth of the ureteral bud into the nephrogenic cord. This view is supported by the fact that no instances are recorded of a formed metanephros in the absence of a ureteral bud. Instances are recorded in which ureteral structures were developed, but no metanephros.

A tenable explanation of bilateral renal agenesis has been offered on the basis of germ plasm defects. Support for this assumption is made in the report of Madisson<sup>3</sup> of two cases of bilateral renal agenesis (not in twins) occurring in fetuses born of the same mother. It is probable that the germ plasm may be deficient in the ability to produce a normal metanephros.

The consummation of the renal system depends upon the formation of the ureteral bud and its subsequent penetration into the nephrogenic mesenchyme. The etiology of bilateral renal agenesis rests on three possible errors of development. The ureteral bud may fail to appear, it may appear, but fail to reach the nephrogenic tissue, or the nephrogenic cap may fail to develop.

*Congenital Solitary Kidney*—Congenital solitary kidney, or unilateral renal agenesis, is a condition brought about by a more or less complete lack of unilateral development of the upper urinary tract, and is much more common than bilateral renal agenesis. As the result of improved diagnostic methods and increased clinical reports, congenital solitary kidney is more frequently diagnosed, especially since the wide use of intravenous urography. In a true case of congenital solitary kidney, no tissue is found on one side that can be identified microscopically as renal parenchyma.

It must be differentiated from the fused kidney, the aplastic kidney, the hypoplastic kidney, as well as from atrophy of the kidney. Gutierrez<sup>4</sup> has classified these different types of undeveloped kidney, and believes that from 35 to 40 per cent of the cases reported as congenital absence of one kidney are not authentic cases. Renal aplasia is considered to be four times more common than unilateral renal agenesis. There are two groups of true solitary

kidney In one group, there is a complete absence of both the kidney and the ureter on one side, the single kidney may be ectopic or cross ectopic, but there is only one ureteral orifice opening in the bladder, and half of the trigone has not developed This anomaly is usually accompanied by some form of congenital malformation, particularly of the genital tract The other group consists of that type of solitary fused kidney in which there is evidence of union of two nephroblastemata into one organ which has two pelves and two corresponding ureters, opening normally or abnormally into the bladder

Autopsy records from various reports indicate that unilateral renal agenesis is found once in about 1,000 postmortems Ten were found in 12,000 autopsies at Cook County Hospital, and ten were found in 13,000 autopsies at Bellevue Hospital (Campbell<sup>5</sup>) Many cases of congenital absence of one kidney have been reported, and the literature has been reviewed by Ballowitz<sup>6</sup> (1895), Moore<sup>7</sup> (1898), Radasch<sup>8</sup> (1908), Anders<sup>9</sup> (1910), Doiland<sup>10</sup> (1911), Eisendrath<sup>11</sup> (1923) Goldstein<sup>12</sup> (1925), and Hennessey<sup>13</sup> (1929) More recently, Collins,<sup>14</sup> in 1932, reviewed the study of 581 cases of congenital unilateral renal agenesis, among which were included nine cases from the Mayo Clinic, found in a series of 6,349 consecutive postmortem examinations He found the incidence of congenital solitary kidney to be 367 in 337,488 autopsies, and one in 920 postmortems Males were more frequently affected (281 to 231), the right kidney is more often absent (238 to 218), and the average age is over 20

Eisendrath and Rolnick<sup>15</sup> mention the following combinations of congenital solitary kidney

(1) Complete absence of kidney, ureter and ureteral orifice on one side This type is the most common, and was present in eight of our cases Hennessey found it present in 273 of 350 cases, and it occurred in over 400 of 581 cases reviewed by Collins It is this type that is also accompanied by other congenital malformations, especially of female genital organs The corresponding half of the trigone was reported as being absent in 44 cases (Collins)

(2) Complete absence of kidney, ureter and ureteral orifice, but the ureter ends at the opposite side of bladder (solitary crossed kidney) They collected four such cases from the literature, and recently, Beer and Ferber<sup>16</sup> reported a similar case

(3) Kidney alone absent Rudimentary ureter, usually short ends in normally placed and developed ureteral orifice This type, with a normal looking ureteral orifice and a ureter of variable length may be overlooked cystoscopically It was found in two of our cases in one, the ureter was about 8 cm long, and in the other, 1 cm long, both ending in a blind pouch The ureter, varying in extent from a short blind pouch to one of normal length, was found in over 10 per cent of the series reported by Hennessey

(4) Complete absence of kidney, ureter, and vesical orifice on one side Opposite kidney, ectopic or pelvic, and the ureter may end in the midline of bladder Eisendrath reported seven, and Hennessey collected two such cases Recently, Stevens<sup>17</sup> reviewed the literature and found 27 cases of pelvic

solitary kidney which included two of his own cases. He stated that true pelvic solitary kidney makes up 4 or 5 per cent of unilateral renal agenesis, and that we may expect to find one case in every 22,000 persons.

*Embryology*—The complete absence of one kidney is best explained by the failure of the ureteral bud to develop. It is not caused by the absence of the metanephric blastema (Hinman<sup>18</sup>). It may be due to early degeneration of the ureteral bud, but this can be proven only when some remnant of the kidney remains. Fortune<sup>19</sup> has proposed four theories as the cause of the condition:

- (1) The metanephric bud may fail to appear in spite of a normal preceding mesonephros.
- (2) The metanephros may appear, but undergo early degeneration.
- (3) The mesonephros may be imperfectly developed.
- (4) The pronephros may fail to develop, and, therefore, the mesonephros does not grow.

The marked frequency with which genital anomalies are found in these cases of unilateral renal agenesis is due to the fact that the corresponding müllerian duct on the agenetic side is absent, and this embryonic defect is responsible for the absence of the genital organs so strikingly seen in females. The müllerian duct develops later than the wolffian duct and the chance for malformation is greater. Genital anomalies were found in three of the ten cases herein reviewed. Hennessey found genital anomalies in one-third of his series, and Collins recorded the presence of malformations of the genital tract in 338 of 581 cases of congenital solitary kidney, 129 being in males, and 209 in females. It is interesting to note that Stevens found genital anomalies in 13 of the 27 cases found, all in females, and in eight cases no mention of genital defect was made by the different writers.

Mention must be made of the significant fact that the adrenal gland has been found to be absent in a certain percentage of cases of unilateral renal agenesis. The cortical portion of the adrenal is derived from the columns of cells which bud off from the wolffian body, and is of mesoblastic origin, while the medullary portion of the gland is developed in connection with the sympathetic nervous system, and is mainly of epiblastic origin. Since the nephrogenic tissues of the wolffian duct are absent and have not developed the kidney, it may be assumed that the adrenal, lacking one of its essential elements, is also absent. Gutierrez suggests a new theory, that when a kidney is not formed, the adrenal on the corresponding side is not formed, and offers this as a differential point of renal agenesis from renal aplasia or hypoplastic kidney, as in the last two conditions the adrenal is invariably present. The adrenal was absent in two of our cases, and not mentioned in eight. Collins stated that it was absent in 66, atrophic in four, normal in 129, hypertrophic in 13, and not stated in 369 cases of the 581 reported. He also states that "the suprarenal glands are not intimately connected with this development (metanephros), and hence are rarely absent even if the kidney or the other related unilateral structures are absent." Eisendrath believes that the adrenal is

TABLE I

ANALYSIS OF POSTMORTEM FINDINGS IN TEN CASES OF CONGENITAL SOLITARY KIDNEY

Case	Age	Sex	Side	Adrenals	Ureter	Bladder	Genitalia	Principal Disease	Kidney
1 L M	40 yrs	F	R	Not recorded	Absent	No orifice	Normal	Huge cyst of ovary, compressing left ureter	Hydronephrosis Hydro-ureter
2 H S	40 yrs	F	R	Not recorded	8 cm long, ending in blind pouch	Dimple	Normal	Carcinoma of breast	Normal
3 M H	38 yrs	F	L	Absent	Absent	No orifice	Hypoplastic left tube and ovary	Uremia	Glomerulonephritis
4 A D	1 mo	M	L	Not recorded	Absent	No orifice	Absent left vas deferens, testicle, and seminal vesicle	Uremia	Fetal lobulations of right kidney with marked dilated calices and ureter
5 J A	10 mos	M	L	Not recorded	Absent	No orifice	Normal vesicle	Broncho-pneumonia	Hydronephrosis, due to aberrant vessel
6 B M	15 mos	M	R	Not recorded	1 cm long, ending in blind pouch	Dimple	Normal cleft palate	Broncho-pneumonia	Hydronephrosis
7 B J	7 hrs	M	R	Not recorded	Absent	No orifice	Undescended testes	Congenital Pulmonary atelectasis	Normal
8 M W	56 yrs	M	L	Not recorded	Absent	No orifice	Normal Hypospadias	Coronary thrombosis	Hyperplasia
9 L A	20 yrs	F	R	Absent	Absent	No orifice	Normal	Uremia	Glomerulonephritis
10 M C	21 yrs	F	L	Not recorded	Absent	No orifice	Normal	Uremia	Glomerulonephritis

RENAL AGENESIS

present in 75 per cent of cases of unilateral renal agenesis. Amolsch found that the supra-renals were rarely affected in bilateral renal agenesis since they were bilaterally absent only twice and unilaterally absent four times in 119 cases. It is difficult to explain this marked difference of opinion in regard to the relationship of the presence or absence of the adrenals in cases of renal agenesis.

The clinical importance of solitary kidney is evidenced in renal surgery, as the literature contains cases of anuria and death following nephrectomy in such cases, as the result of errors in diagnoses. The diagnoses of congenital solitary kidney will never be missed if ureteral catheters are employed in every instance and a check-up is made by excretory urography. The solitary single kidney is anatomically and physiologically enlarged, owing mainly to the compensatory functional hypertrophy. It is of great importance to note that a congenital solitary kidney is not a serious menace to life unless a genito-urinary tract disease is present, and then a much poorer, if not fatal, prognosis is offered. Sixty-eight point three per cent of the patients in Collins' report expired from diseases totally unrelated to the genito-urinary system. In this series, a marked hydronephrosis was found in Cases 1 and 5, and glomerulonephritis was present in Cases 3, 9 and 10. Among the diseases of the kidney mentioned as the cause of death, in order of frequency, are renal and ureteral calculus, pyelonephritis and pyonephrosis, chronic nephritis, hydronephrosis, renal tuberculosis, and stricture of the ureter.

Conservative measures are usually employed to treat obstructive and infective conditions of a congenital solitary kidney, but in cases of impending uremic symptoms, as in renal or ureteral calculi (anuria), or pyelonephritis or pyonephrosis, surgery must be resorted to immediately. A pyelotomy or nephrostomy, to establish drainage, has often been a life-saving procedure.

#### SUMMARY

- (1) Twelve cases of renal anomalies found at postmortem are reported.
- (2) Two cases of bilateral renal agenesis are recorded, making the total number of cases reported 121.
- (3) Bilateral renal agenesis occurs in about one out of 6,000 autopsies.
- (4) Ten cases of congenital solitary kidney are recorded in which the kidney, ureter and ureteral orifice were absent in eight cases, rudimentary ureters were present in two cases, associated genital anomalies were found in three, and the adrenal gland was absent in two and not recorded in eight cases.
- (5) Bilateral renal agenesis is usually found at autopsy, but unilateral renal agenesis is diagnosed more frequently, and proper treatment instituted much earlier than previously, as the result of improved diagnostic methods and a more general employment of intravenous urography.

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# DERMOID CYST OF THE BLADDER

## CASE REPORT

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FROM THE SURGICAL CLINIC OF THE STEFAN BATORZY UNIVERSITY OF WILNO, WILNO, POLAND  
PROF DR K. MICHEJDA, DIRECTOR

DERMOID cysts of the bladder are extremely rare. The number of cases thus far published does not exceed 15. They may exhibit symptoms of cystitis and offer as a pathognomonic sign, the discharging of hairs on urination (pilimictio). They may occur as a tumor protruding into the bladder cavity, or as a paravesical cyst, which invades the bladder and communicates with it through a small channel, as was the case in the present instance. The treatment consists in the removal of the cyst, either by an intra- or extravescical procedure, or by a combined approach. In the case herewith reported, the dilating of the communicating fistulous tract and the removal of the contents of the cyst caused its reduction to the size of a small diverticulum and to a subsidence of the pathologic process in the bladder, followed by clinical recovery.

**Case Report**—B. M., white, female, age 30, single, nullipara, was admitted to the University Clinic February 1, 1938, complaining of frequency, pain on urination and the passage of fetid, turbid urine. The present illness had begun four months previously. She had remained in bed for two weeks before consulting a doctor. During the ensuing three and one-half months, all local and medicinal measures proved ineffectual and the frequency and dysuria had increased. Her family and previous history were irrelevant.

**Physical Examination**—The patient was well proportioned but poorly nourished. Temperature 39° C, pulse 125. Palpation of the suprapubic region was painful. Examination of the chest and abdomen was negative. WBC 8,100. Urine Turbid, alkaline, fetid, sp. gr. 1.015, the sediment contained red and white blood cells and ammonium-magnesium phosphate crystals. Cystoscopy could not be performed because of the small capacity of the bladder and the intolerance of the patient, who ejected all fluids introduced intravesically. It was noted, however, that the cystoscope met with a definite resistance.

**Roentgenologic Examination** showed a dense mesial shadow behind the pubes and another smaller one, of irregular density, partially superimposed upon the right upper aspect of the denser shadow (Fig. 1). A cystogram showed that the first shadow did not alter while the second became considerably larger and its contour more definite (Fig. 2). **Preoperative Diagnosis** Calculosis vesicae.

**Operation**—Under local anesthesia, a suprapubic incision disclosed a hard, yellow stone, the size of a walnut, weighing 12 Gm. This was extracted from the bladder. Looking further for the source of the other shadow on the roentgenogram, the forefinger encountered an opening about  $\frac{1}{4}$  cm. in diameter to the right of the internal orifice of the urethra. The opening was dilated with the forefinger to a diameter of 1.5-1.5 cm., and enabled the forefinger to enter a cavity which was found to contain a foreign body. This, upon removal, proved to consist of a ball of hair the size of a small walnut, partially covered with a phosphatic deposit (Fig. 3). A tampon was inserted to the reflection of the peritoneum from the bladder and into the prevesical space. The wound was sutured with the exception of the cystostomy opening into which a Pezzer catheter was placed.

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The physicochemical and microscopic analyses of the stone showed it to be of homogeneous structure and composed of ammonium-magnesium phosphates

*Subsequent Course*—The patient made an uninterrupted recovery. The tampons were removed on the sixth day after operation. On the eighth day, the sutures were removed. The Pezzer catheter was taken out on the twelfth day and a Nelaton catheter *a demeure*



FIG 1—Primary roentgenogram showing a dense, mesially situated homogeneous shadow, and a second one of irregular density, partially superimposing the right upper aspect of the first shadow

FIG 2—Preoperative cystogram. There was no alteration of the denser, mesial shadow, but the second more poorly defined shadow became considerably larger and its contour and anatomic relations much more definite

introduced through the urethra. Urine ceased to come through the cystostomy wound on the fourteenth day and was discharged exclusively through the catheter. The catheter *a demeure* was removed on the seventeenth day. At the end of two weeks, the cystostomy wound had healed completely. The urine still contained red and white blood cells, but the symptoms of cystitis had ceased and the patient, who had been bereft of sleep and had frequently had to void small amounts of fetid, turbid urine, accompanied by intense pain, began to pass a clear odorless urine five to six times during the 24 hours.

#### *Postoperative Cystoscopic Examination*—Bladder contents 300 cc,

mucous membrane reddened, vessels blurred, both ureter orifices normal. Intravenous indigo carmine returned in seven minutes in good concentration from each kidney. In addition, on both sides of the orifice of the right ureter and a little above it, two small excavations were seen, one the size of a small bean, the other the size of a pea, and between them a third small crater-like excavation with somewhat everted, folded edges. Probing with an ureteral catheter showed that the lateral excavations were very shallow,  $\frac{1}{4}$  cm deep, while the catheter could be introduced a distance of 3 cm into the middle orifice. A



FIG 3—Photograph of the gross specimens removed from the bladder and the cyst cavity, arranged in their relative positions

cystogram, employing 60 cc of 10 per cent abrodil, revealed the shadow of the bladder to be the shape of an equilateral triangle with a truncated apex pointing upwards and a small spherical shadow, situated to the right of the base line, which apparently connected with the bladder cavity and was interpreted as representing the contracted cyst which had originally contained the hair ball (Fig 4)



FIG 4—Postoperative cystogram. The residual, contracted cyst is represented by the small spherical shadow, situated to the right of the base line of the vesical shadow

#### SUMMARY

A female, age 30, suffering from an intractable cystitis, was impossible to cystoscope. Roentgenologic examination showed two shadows in the pelvis. Cystostomy revealed that one of the shadows corresponded to a stone, the other to a hair ball. The latter lay in a diverticulum which represented a paravesical dermoid cyst which had opened into the bladder. The cystovesical, fistulous tract having been dilated and its contents removed, the cyst became practically obliterated.

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# CYSTS OF THE URACHUS

## REPORT OF TWO CASES

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THE URACHUS is a structure which passes upward from the bladder toward the umbilicus. It is frequently referred to in anatomies as the middle umbilical ligament.<sup>1 2</sup> Begg<sup>3</sup> has demonstrated that it is normally incompletely patent throughout life, and in several cases a continuation of the bladder mucosa into the urachus has been found. It is subject to the same pathologic processes which are noted elsewhere, namely, maldevelopmental, inflammatory, neoplastic and degenerative.

The most frequent abnormalities which are seen are (1) Anomalies in development, (2) cyst formations, which may at times be related to congenital defects. Long<sup>4</sup> has classified cysts of the urachus into four anatomic groups:

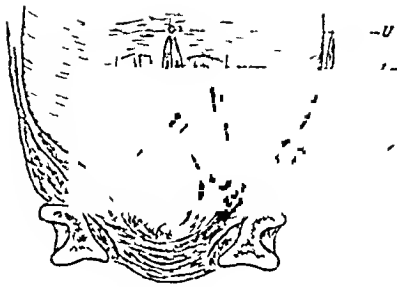
- (I) Those which communicate with the bladder
- (II) Those which communicate with the umbilicus
- (III) Those which communicate with the bladder and with the umbilicus, forming vesico-umbilical fistulae
- (IV) Those which do not seem to communicate with either (Plate I)

The present communication will confine itself, for the most part, to Group IV. These patients frequently present the diagnostic problem of differentiating a midline suprapubic mass which is only slightly movable. As infection is usually present, the mass is tender to palpation and the patient may appear acutely ill. The diagnosis is often made at the operating table, and the procedure to be performed is usually decided upon at this time.

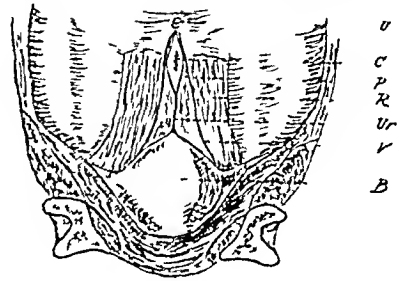
Cysts belonging to the other groups will be considered if, due to closure of their drainage tract, they become potentially Group IV cases.

*Incidence*—The incidence of cysts of the urachus is rather small. Young<sup>5</sup> reports only three cases in 12,500 admissions to the Brady Urological Institute. We have records of only four cases during the past five years. In 1886, Lawson Tait<sup>6</sup> presented 12 cases of suprapubic cysts, several of which were without doubt urachal in origin. They were all described as lying extraperitoneally. In two of these cases, excision was attempted, which resulted in immediate postoperative fatality. In the remainder, incision and drainage were effected, with no immediate mortality, although several deaths were later noted. Among the cases which lived, Tait did not describe any subsequent recurrences. He was probably the first surgeon to diagnose this condition preoperatively.

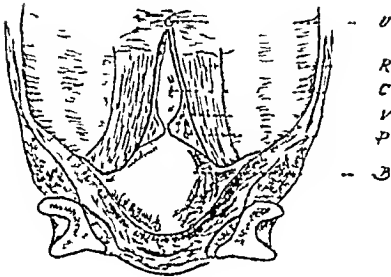
A complete analysis of the reported cases was published by Weiser,<sup>8</sup> in 1906. He states that, in 1648, Pea described a mass in a newborn child which



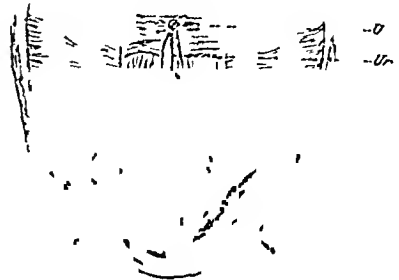
GROUP I



GROUP II



GROUP III



GROUP IV

PLATE I—Schematic drawings illustrating the four anatomic groups as suggested by Long.<sup>1</sup>  
 U Umbilicus Ur Urachus R Rectus muscle P Peritoneum C Cyst V Umbilical vessels  
 B Bladder

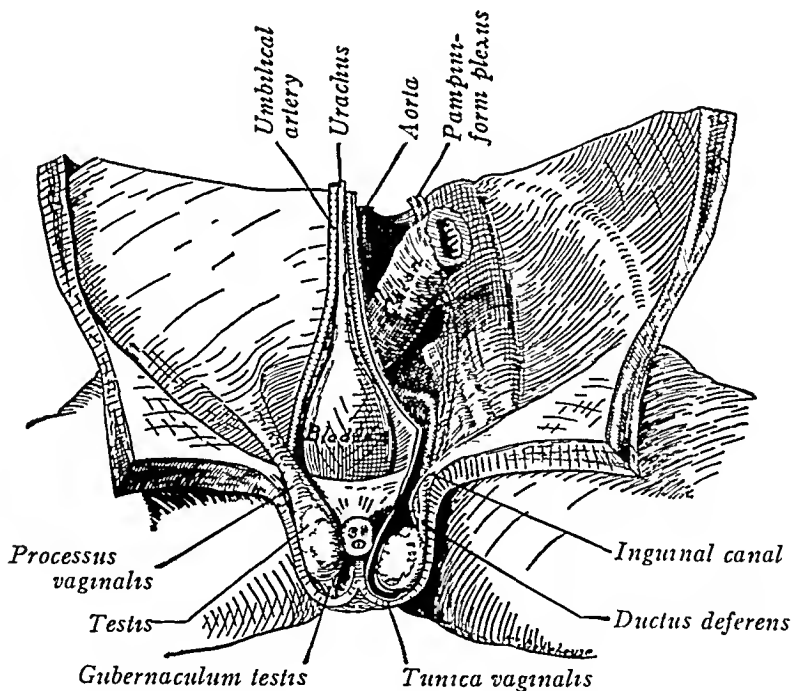


FIG 1—Ventral dissection of a nearly full-term fetus to demonstrate the relation of the descended testis to the processus vaginalis (after Corning). On the right the peritoneum is intact, on the left the peritoneum and its scrotal sacculization have been opened and the testis rotated 90°. (After Aron L. B. Developmental Anatomy, 2nd Ed W B Saunders Co, Phila, p 244, 1931)

may have been due to a cyst of the urachus. The reports in the early literature were collected by Wutz,<sup>7</sup> in 1883. However, many of these early descriptions were considered inadequate for a positive diagnosis.

*Embryology, Anatomy and Pathology*—The bladder is formed from the ventral portion of the cloaca, and is mesodermal in origin.<sup>9</sup> With growth and development, it later occupies a roughly triangular space with its apex at the umbilicus (Fig. 1).

The elongated apex, continuous at the umbilicus with the allantoic stalk, is the urachus.<sup>10</sup> As the bladder and the urachus descend, the attachment to the umbilicus is retained either as a fascial plexus or as a fibrous cord. Embryologically, the vesical epithelium is continuous into the urachus. This

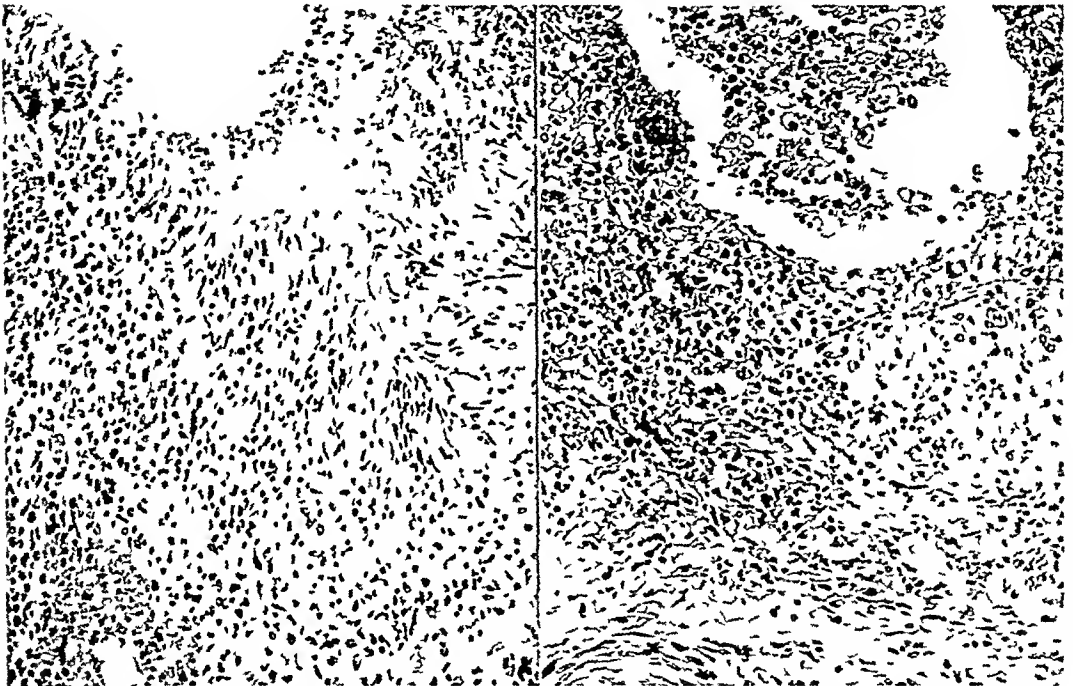


FIG. 2—Case 1. Section of biopsy. Photomicrograph demonstrating replacement of epithelial lining by granulation tissues showing evidence of inflammation.

FIG. 3—Section of specimen removed at autopsy. Photomicrograph showing evidence of inflammation and absence of epithelial lining of urachus.

was also confirmed in the comparative studies made by Rossi.<sup>11</sup> The lumen of the urachus is never entirely obliterated, and occasionally secretory cells have been demonstrated in the mucosa. Begg<sup>12</sup> has also pointed out that there is a more or less constant tendency for epithelial desquamation.

In considering the pathogenesis of cysts, two possibilities may be pointed out. There may at times be protrusion of mucus-secreting cells into the wall of the urachus. These are shown in Begg's<sup>12, 13</sup> sections. Probably the more common method is the closure of the lumen by debris, with accumulation of secretions and consequent cyst formation.

At operation, most of the cysts are obviously infected. In those forming Group IV, it is interesting to speculate as to the avenue of infection. Hematogenous and lymphogenous spread have been suggested, and these possibilities

are not to be denied. However, with previous communication with the bladder demonstrated, direct extension seems plausible in most cases. The tract may not be demonstrated because of subsequent obliteration. Powell<sup>11</sup> reported a case where, with closure of the urachal communication with the bladder, an infected cyst was formed. This case was cured by incision and drainage.

Cultures from infected cysts are not infrequently reported sterile. However, this is in accord with localized infections elsewhere which, after a period of time, may become sterile. *Bacillus coli communis*, *Streptococcus* and *Staphylococcus* have been reported present.

Microscopic study of a section of cyst wall from Case I showed the replacement of the mucosa by inflamed granulation tissue (Fig 2). In the study of an infected cyst of the urachus noted as an associated finding during a recent autopsy, it was again found that the mucosa was replaced by granulation and fibrous tissue (Fig 3). This probably accounts for the frequent absence of recurrence following incision and drainage of infected cysts.

*Surgical Procedure*—In reviewing the literature on cysts of the urachus, one finds that the diagnosis is usually made at operation. Following the usual suprapubic incision the mass is observed to be extraperitoneal, and its origin from the urachus is frequently obvious. Because of the conception held by several surgeons that complete extirpation is necessary for cure, the following case is presented.

## CASE REPORTS

**Case 1**—M. R., female, age 2, was admitted July 23, 1937, to the service of Dr. E. Beer, Mount Sinai Hospital. Her mother stated that for the past week the child had appeared ill. She had vomited several times, but no fever was noted. For two days prior to admission, the child cried during and after urination. Temperature 101.2° F. For 24 hours, the child had voided small quantities, and catheterization yielded about five ounces of "strong-smelling" urine. After completely emptying, the physician noted that the "bladder remained tense." Past history was irrelevant. There had been no illnesses related to the urinary tract.

*Physical Examination* revealed an acutely ill, fretful child. Except for the abdominal findings, no abnormalities were noted. In the suprapubic region, and extending midway to the umbilicus, was a round, somewhat tender, cystic mass about the size of an orange. It was not freely movable, but could be displaced slightly from side to side. During the examination, the child expressed a desire to void, and passed about 20 cc. of clear urine. There was no apparent pain during micturition. The mass descended slightly toward the symphysis but did not decrease in size. Urinalysis and blood chemistry normal. Wassermann reaction negative. A plain roentgenogram of the abdomen and a pyelogram, following injection of hippuran intravenously, were reported normal.

*Cystoscopic Examination*—Dr. M. Swick. As the bladder was filled, it was noted that the mass, retaining its original size, rose upward toward the umbilicus. The bladder mucosa was entirely normal, and no diverticula were seen. As the bladder was emptied there seemed to be intrusion of an extravescical mass on the superior wall of the bladder. This was coincident with the descent of the mass as noted abdominally. Dr. A. H. H. suggested an infected urachus cyst among the possible diagnoses.

*Operation*—A midline suprapubic incision was made into a cyst which contained about eight ounces of thick, creamy pus. Evacuation of the contents revealed a smooth-walled cavity from which a biopsy was taken. The cyst was drained. *Pathologic Diag-*

## CYSTS OF THE URACHUS

*notes* Dr Paul Klemperer Biopsy specimen Inflamed, fibrous cyst wall (Fig 2)  
Culture Negative

Convalescence was uneventful The patient was discharged August 4, 1937, the seventeenth postoperative day, with the wound practically healed

When seen in the Follow-Up Clinic, six months later, the scar was firm and there was no evidence of recurrence or herniation The cure effected by this simple procedure was unquestioned

The following case of Dr A A Berg is reported

**Case Report**—S M, male, age 29, physician, was admitted to the Mt Sinai Hospital March 20, 1935, complaining of a tender, suprapubic swelling, which had been present for some time There was a persistent low grade fever, and he had suffered some loss of weight *Preoperative Diagnosis* Suppuration of the urachus

*Operation*—Dr A A Berg The mass was incised by a suprapubic midline incision, and several loculated abscess cavities were found These contained foul-smelling pus, and drainage was instituted

Convalescence was complicated only by persistent drainage from a remaining sinus The patient was discharged, April 20, 1935, in good physical condition However, the sinus continued to drain, and the patient was readmitted June 23, 1935, for excision of the tract At this operation it was noted that, except for one small pocket of pus, the wound was clean and healed Fibrous and granulation tissue had completely obliterated the cavity It was suspected that the sinus led down to the bladder, and excision of the cyst was performed A connection with the bladder could not be demonstrated during the procedure The postoperative course was again complicated by continued drainage from the wound At the end of several months, the wound showed no evidence of closing, and the drainage still continued to be profuse The sinus tract was now injected with radiopaque oil, and roentgenologic examination demonstrated a communication with the bladder and a branching sinus running into the abdomen toward the ileocecal region The urine was grossly infected, and the sinus discharge was foul

The patient was readmitted to the hospital for an exploratory celiotomy At operation, the intra-abdominal sinus was traced to an old gangrenous appendicitis with abscess cavity This was removed with great technical difficulty To control the severe cystitis, suprapubic cystotomy was performed The patient improved rapidly, and was discharged October 2, 1936 The sinus leading to the base of the appendix was closing, and the patient's condition was good

*Follow-Up* Convalescence was uneventful except for the persistence of a small fecal fistula, which is still present Its etiology has remained somewhat obscure, and the patient is to be restudied His health has remained excellent and there have been no residual urinary symptoms

The patient, in retrospect, dated the onset of the appendicitis to an attack of severe right lower quadrant pain which he had suffered some time prior to the third operation However, Dr Berg's description of the healing wound, present at the time of the second operation, clearly indicated the advantage of this initial procedure

A review of the reported cases of cyst of the urachus proved most interesting in determining the necessity of complete excision of the cyst for permanent cure Because of changes in operating room technic, only cases reported since the publication by Weiser<sup>8</sup> are presented in the table Group IV cases were chosen because the diagnosis was usually obscure and the operative technic of excision is frequently difficult



TABLE I  
CYSTS OF THE URACHUS REPORTED IN THE LITERATURE FROM 1907-1936

No	Reported by	Year	Age	Sex	Group	Diagnosis	Infection	Operative Procedure	Result	Drainage Period	2nd Operation
1	Macdonald <sup>16</sup>	1907	40	F	IV	Operation	?	Excision*	Cured	—	—
2	Doran <sup>17</sup>	1908	17	F	IV?	Operation	No	Excision of anterior wall Drained	Cured	Not stated	—
3	Arrou <sup>18</sup>	1910	?	M	II?	Preoper	Yes	Excision	Cured	—	—
4	Cullen <sup>19</sup>	1910	15	M	IV	Operation	Probable	Incised and drained	Cured	—	—
5	Weber <sup>20</sup>	1910	26	F	IV?	Operation	?	Excision	Cured	Not stated	—
6	Baldwin <sup>1</sup>	1911	6	F	IV?	Operation	No?	Incised and drained	Cured	Brief	For incisional hernia
7	Baldwin <sup>1</sup>	1901	33	F	IV	Operation	Yes	Incised and drained	Cured	Prolonged Cyst large	—
8	Means <sup>2</sup>	1914	32	M	IV	Preoper	No	Excision	Cured	—	—
9	Boni <sup>3</sup>	1914	23	M	IV	Preoper	No	Excision	Cured	—	—
10	Jacoby <sup>4</sup>	1915	33	F	IV	Operation	No	Anesthetic death	—	—	—
11	Morene <sup>5</sup>	1915	17	F	IV	Preoper	Yes	Incised and drained	Cured	3 mos?	—
12	Gramen <sup>6</sup>	1916	41	M	IV	Operation	Yes	Excision	Cured	—	—
13	Aleman <sup>27</sup>	1916	51	M	IV	Operation	Yes	Excision?	Died	—	—
14	Ward <sup>8</sup>	1918	44	F	III?	Preoper	Yes	Incised and drained Concretion removed	Cured	10 days	—
15	Davis <sup>9</sup>	1919	33	M	{ I? IV? }	Preoper	Yes	Excision	Cured	14 days	—
16	Bua <sup>30</sup>	1920	35	F	IV?	Operation	?	Excision*	Cured	—	—
17	Edington <sup>11</sup>	1921	50	M	IV	Operation	No	Excision*	Cured	—	—
18	DeCastro <sup>3</sup>	1926	24	F	IV?	Operation	Yes	Excision*	Cured	—	—
19	Rankin and Parker <sup>33</sup>	1926	55	F	IV?	Operation	Yes	Excision	Died	—	—
20	Rankin and Parker <sup>33</sup>	1926	20 mos	F	{ I? IV? }	Probable	Yes	Drainage tract dilated	Not followed	—	—
21	Lubash <sup>41</sup>	1929	22	M	II?	Preoper	Yes	Emergency excision	Cured	Prolonged	—
22	Denneen and Margold <sup>3</sup>	1929	43	M	IV	Operation	Yes	Celiotomy for peritonitis	Died	—	—
23	Ronald <sup>46</sup>	1929	26	M	IV?	Operation	No	Excision	Cured	—	—
24	Tassovatz <sup>37</sup>	1930	23	M	{ II? IV? }	Operation	Yes	Excision	Cured	Brief	—
25	Siddall <sup>38</sup>	1931	24	F	IV	Operation	No	Incomplete excision	Cured	Brief	—
26	Long <sup>4</sup>	1931	5	M	IV?	Preoper	Yes	Incised and drained	Cured	3 wks	—
27	Long <sup>4</sup>	1931	6	M	II?	Preoper	No	Excision	Cured	Brief	—
28	Long <sup>4</sup>	1925	27	F	IV?	Operation	Yes	Spontaneous rupture Drained	Cured?	Brief	—
29	Bauer <sup>39</sup>	1931	47	F	IV?	Operation	?	Excision	Cured	—	—
30	Schmidt <sup>40</sup>	1933	24	M	IV?	Operation	No	Excision	Cured	—	—
31	Rives <sup>41</sup>	1933	?	M	IV?	Preoper	Yes	Incised and drained	Improved	2 mos	Excision
32	Stevens <sup>42</sup>	1933	24	M	IV?	Preoper	Yes	Excision	Cured	—	—
33	Lazarus and Rosenthal <sup>43</sup>	1933	51	M	IV	Operation	Yes	Excision	Died	—	—
34	Ginsburg and Nixon <sup>44</sup>	1934	2	F	IV	Preoper	Yes	Excision	Peritonitis?	—	—
35	Gayet and Verniere <sup>45</sup>	1935	69	M	IV?	Operation	Probable	Excision*	Peritonitis	—	—
36	Lavand homme <sup>46</sup>	1936	22	F	IV?	Operation	Yes	Incised Cyst marsupialized	Improved	1 mo	Incomplete excision Curettement

\* Operation reported to be technically difficult. Bladder opened in some cases. Closure of the abdomen was occasionally inadequate.

## CYSTS OF THE URACHUS

### EXPLANATORY NOTES RELATIVE TO CASES CITED IN TABLE I

Case 1—Excision undertaken only because of suspicion of carcinoma, not corroborated by microscopic study Procedure difficult and postoperative course stormy

Case 2—Excision not practical Posterior cyst wall left

Case 6—Patient reoperated upon four months later for incisional hernia The note of the surgeon's findings are recorded elsewhere

Case 10—On attempted excision at postmortem, the surgeon stated it would have been too difficult to perform

Case 21—At previous celiotomy, the cyst was said to have ruptured intraperitoneally, and drainage was instituted Injection of the sinus for roentgenologic purposes resulted in peritoneal reaction and immediate excision was performed Convalescence was stormy

Case 22—At celiotomy, peritonitis was found Autopsy revealed its etiology to be an unusual intra-abdominal perforation of an infected urachus cyst

Case 31—Continued drainage of serous fluid was not explained Secondary excision was reported as having been relatively easy

Case 33—Celiotomy was performed first, with negative findings Mass was excised and pus was noted to extend into the groin Anuria developed, with death from uremia

Occasionally where portions of cyst wall were left, various methods for cauterization were employed

### ANALYSIS OF CASES CITED IN TABLE I

Seven cases of cure following incision and drainage of the cyst were recorded In all but one, infection was definitely present Three cases of incomplete excision with cures were noted No recurrences in these cases have been reported

Four cases with fatality subsequent to excision are recorded In three of these, peritonitis was given as the cause of death

Four cases of excision secondary to initial incision and drainage were presented In three of these, complicating features as noted may have prevented normal healing

In many of the reports, where primary excision was performed, technical operative difficulty was noted Adherent peritoneum was frequently excised, with occasional difficulty in closure The bladder was opened in several instances In one report, attempted excision would have been futile

Case 6 (Baldwin<sup>21</sup>), reoperated upon for incisional hernia, four months after incision and drainage, the surgeon stated "The sac had entirely disappeared and nothing was found to suggest previous trouble in the abdomen"

SUMMARY—(1) Cysts of the urachus are conveniently classified by an anatomic grouping

(2) A review of the Group IV cases, from the recent literature, is presented

(3) Two additional cases are reported

(4) Microscopic sections demonstrating destruction of the epithelial lining of the urachus in the presence of infection are shown

### CONCLUSIONS

It is suggested that where the diagnosis of infected urachus cyst is made, incision and drainage may be adequate to effect a cure

Where reoperation may be necessary, subsequent excision is more easily and safely performed

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# WHOLE-THICKNESS GRAFTS IN CORRECTION OF CONTRACTURES DUE TO BURN SCARS\*

## THREE CASE REPORTS

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THE surgical correction of a deformity of the trunk or extremity resulting from the contractural effect of a deep burn scar presents a most difficult problem. Because of the continued contracture of such a cicatrized area, the scars overlying joints tend to cause increased deformity in time and, in young subjects, the growth of the individual may contribute toward the development of crippling disability. The continued trauma coincident to locomotion or other exercise causes these unstable scars to ulcerate readily. The epithelium overlying the scar is thin, the blood vessels are few, and stretching of the scar in an attempt to correct the deformity, as is often practised in the methods of physical therapy, produces ischemia which may be followed by ulceration.

In cases in which the scarred area is not too large the thickened scars may be excised completely and the superficial defect repaired with large grafts of skin. Blair and Brown<sup>1</sup> have advanced this form of treatment, and have reported many cases in which large scars have been completely replaced by thick-split grafts of skin. When, however, complete excision of the scarred tissue is not feasible by reason of the magnitude of the deformity or the paucity of cutaneous areas from which grafts may be cut, some other method must be adopted. In such cases it has been my practice to combat the contractural effect of the scar by the interposition of an elliptically shaped, whole-thickness, free graft of skin at a strategic point in the line of pull of the scar. A simple, linear, relaxation incision is made in such a way as to divide the scar at the point where it exerts greatest force. Such an incision establishes an elliptical, gaping wound into the floor of which the normal fatty or muscular tissue bulges. Scar tissue remnants are dissected away from the edges of the wound. A whole-thickness, free graft of skin, patterned to fit the defect, is introduced. The graft is sutured accurately into place and held immobilized by a dressing incorporating sponge rubber. Because the successful transplantation of large, whole-thickness grafts of skin depends largely on complete immobilization of the wound in the early postoperative period, a suitable plaster spica is applied. The reward of adequate postoperative immobilization of the area is a complete "take" of the graft. When healed, the transplantation forms an elastic bridge at the midpoint of a contracture upon which both sections of the scar may exert their force. Because of its elasticity, its mobility, and

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its resistance to potential contractions, the whole-thickness graft of skin is preferred, although the details of operation and after-care are more burdensome than those of the Olhert-Thiersch or thick-split graft. Split grafts of skin, if applied to a soft tissue surface, undergo contraction evidenced by the development of wrinkles on the surface of the graft and by the subsequent decrease in width of the original relaxation incision.

#### ABBREVIATED CASE REPORTS

**Case 1**—N Y Hosp No 73967 Massive burn scar of lower abdomen, groin and upper thigh, causing flexion contracture of thigh. H H, male, age 10, while playing with fireworks, had been severely burned, five years previously, when his clothes caught fire. Examination, August 28, 1934, showed an extensive scar, measuring 32 cm vertically and 20 cm transversely, which extended from the midabdomen down to the midportion of the left thigh. Flexion deformity of the thigh measured 30 degrees. The scar was hard, pale and greatly thickened (Fig 1).

*Operation*—August 27, 1937 Under ether anesthesia a "relaxation" incision, 12 cm long, was made parallel to Poupart's ligament. All the scar tissue was dissected away from the floor of the resultant elliptical wound, exposing the loose, areolar tissue overlying the femoral artery, vein and nerve. A whole-thickness graft was cut from just above the crest of the right ilium, according to a pattern of the wound, the resultant cutaneous defect being obliterated by undercutting the flaps and approximation of the edges. The graft was accurately sutured into place in the left inguinal region. A dressing, incorporating sponge rubber, was applied and immobilization was accomplished by means of a plaster hip spica. The graft was successfully transplanted, and "took" in its entirety. The patient was discharged on the seventeenth day postoperative.

*Subsequent Course*—The flexion contracture of the thigh had been relieved (Fig 2), the scar tissue above and below the graft had become softer and apparently thinner. Through the graft, the structures in the femoral triangle could be easily palpated.

**Case 2**—N Y Hosp No 28343 Massive burn scar of right trunk and right thigh, causing partial scoliosis and flexion contracture of the thigh. M C, female, age 12, had been severely burned six years previously, when her clothing caught fire. Examination, February 2, 1937, showed extensive, deep scars running from the scapular and axillary regions down the thoraco-epigastric region to the lateral and anterior aspects of the right thigh. A linear band of scar tissue was noted in the thoracolumbar region. Just inferior to the crest of the ilium, the scar was very thick and at this point it was adherent to the underlying bone (Fig 3).

*Operation*—December 21, 1937 Under ether anesthesia, "relaxation" incision, 10 cm long, was made over the crest of the ilium. All scar tissue was dissected away from the floor of the resultant elliptical wound. A whole-thickness graft of skin, measuring 4x11 cm, was cut from the region of the left gluteal fold, according to a pattern of the wound. The graft was sutured in place and the donor site was closed by primary suture. Guttapercha was placed over the graft and moderate pressure was made on it by tight adhesive strapping over a layer of rubber sponge. Immobilization of the extremity and lower torso was accomplished by means of a plaster hip spica. The graft was successfully transplanted (Fig 4), except for an area, 2x2 cm in size, in its anterior portion where complete sloughing occurred. This was apparently due to the marked ischemia of the adjacent scar. A Z-plastic operation was performed in the lateral thoracic region (Fig 5). The patient was discharged on the twenty-fifth day postoperative.

*Subsequent Course*—The scoliosis has been corrected (Fig 5). The flexion contracture of the thigh will be cared for subsequently.

**Case 3**—N Y Hosp No 182097 Annular burn scar of thigh of 22 years' duration, with ulceration and impairment of venous circulation of the leg. F G, male, age 34, re-



FIG 1—Case 1. Massive burn scar of lower abdomen and thigh. The scar was hard pale and approximately 2.5 cm deep. Extension of the thigh was limited 30 degrees. On forced extension of the thigh the scar became white in the area overlying Poupart's ligament.

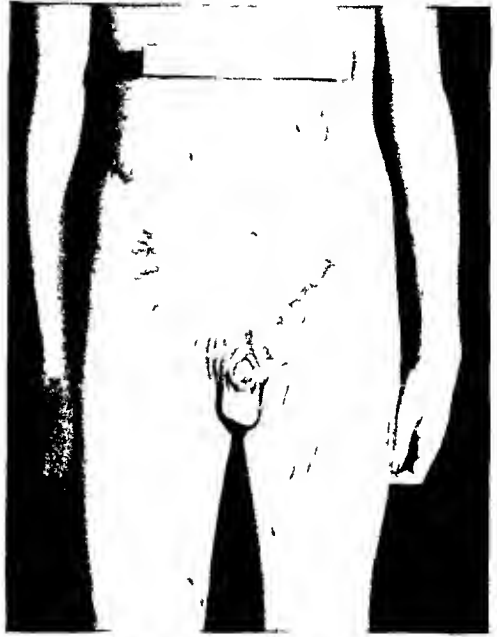


FIG 2—Case 1. Whole thickness graft in place where relaxation incision was made over Poupart's ligament. After operation the scar became softer and thinner and extension of the thigh was no longer limited.



FIG 3—Case 2. Dense burn scar of right thoracic and abdominal wall and right thigh. Scoliosis and limitation of extension of the thigh were the major deformities.



FIG 4—Case 2. Photograph taken after operation to show the extent of the whole thickness graft of skin. The pull of the scar tissue band in the anterior portion of the thigh, will be corrected at a future operation.

ceived severe dynamite burns of the right thigh at age 12. He was hospitalized for 13 months, during which time skin grafts were applied to the wound on several occasions, without success. Six years elapsed before the wound was entirely covered with scar epithelium. Four years ago, the patient was accidentally cut on the outer aspect of the right thigh. The ulcer which resulted persisted until the time of his admission to the New York Hospital. The patient had moderately severe diabetes.

Examination, March 3, 1938, showed an extensive deep scar of the anterior and lateral aspects of the upper right thigh. Its contractural effect was evidenced by an annular depression of the inner and posterior aspects of the thigh and the numerous large varicosities below the level of the scar. On the lateral aspect of the scar, there was a punched-out ulcer, 2.3 cm in size (Fig. 6). Over the anterior thigh, a small sinus discharged frag-

FIG 5

FIG 6

FIG 7

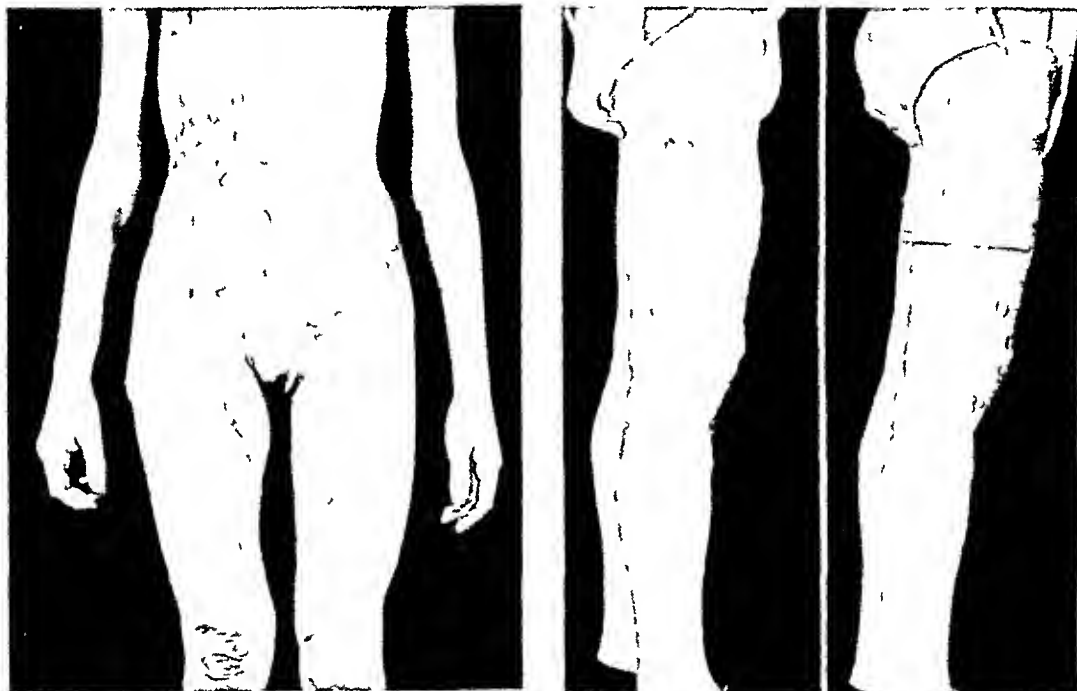


FIG 5—Case 2. Photograph taken after Z-plastic operation upon lateral abdominal area, "relaxation" incision just below the crest of the ilium, and insertion of an elliptical, whole-thickness graft of skin. Note the correction of the curvature of the spine.

FIG 6—Case 3. Annular burn scar of the leg, with ulceration and obstruction to the superficial veins causing varicosities. Scar had been present for 22 years.

FIG 7—Case 3. Photograph taken 30 days after operation at which time the ulcer was excised, "relaxation" incision was made, and whole-thickness graft of skin was introduced. The diminution in the extent of the varicose veins is very striking.

ments of calcified fibrous tissue. Extension of the thigh in walking caused pallor of the scar.

**Operation**—March 18, 1938. Cyclopropane anesthesia. After adequate alkalinization of the ulceration and regulation of the diabetic state, the ulceration on the lateral aspect of the thigh was removed by an elliptical incision. The scar tissue was 1.2 cm thick. A "relaxation" incision, 18 cm long, was made parallel to the long axis of the thigh. The floor of the wound was freed of fibrous tissue, so that healthy, adipose tissue bulged into the defect. An elliptical free graft of the whole-thickness of skin was cut from the right lateral abdominal region according to a pattern of the wound. The donor wound was closed by linear approximation of the edges of the skin after adequate undercutting. The graft, measuring 8x20 cm, was sutured into place in the wound on the thigh and held immobilized by a dressing incorporating sponge rubber. A plaster hip spica was applied. The patient was discharged on the thirtieth day postoperative.

**Subsequent Course**—On opening the dressing, 12 days after operation, it was apparent



that the graft had taken. Two small areas showed superficial sloughing. The patient was allowed to walk about after four weeks of bed rest. There was a complete release of tension in the thigh, the varicosities were less in evidence (Fig. 7), and the patient enjoyed much greater freedom of motion in the extremity.

**DISCUSSION**—The interruption of a contracture due to a burn scar by "relaxation" incision, and the insertion of a whole-thickness free graft of skin, has been found to be an effective method of correcting skeletal deformity due to burn scars. This method of surgical treatment was referred to by Davis,<sup>2</sup> as early as 1917. Since then, the surgical literature has shown so many reports of the treatment of dense burn scars by the use of pedunculated flaps of skin and subcutaneous tissue, that the impression prevails that such deformities cannot be corrected without long periods of hospitalization and operation in several stages. The method employed in these three cases is most ideally applicable to scars about the trunk and extremities in which a maximal, functional end-result is the aim, and the cosmetic result is relatively unimportant.

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# PILONIDAL SINUS

## SACROCOCCYGEAL ECTODERMAL CYSTS AND SINUSES

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CYSTS occurring in the sacrococcygeal region having cutaneous openings on the skin surface are of frequent occurrence. These sinuses and cysts have been grouped under the inappropriate and nondescriptive term, "pilonidal sinus." The term "pilonidal" is derived from the Latin and simply means a hair nest. Hair nest has no significance and is certainly not descriptive of this interesting clinical entity. Most authors agree regarding the etiology—namely, that these cysts and sinuses result from a maldevelopment of the ectoderm—but they disagree as to the primitive structure from which they originate. As a more descriptive term is desirable, the author proposes the name "sacrococcygeal ectodermal cysts and sinuses." The term denotes not only the character of the lesion but its derivation as well. This descriptive phrase can with equal lucidity be applied to both the sacrococcygeal sinuses and sacrococcygeal dimples.

Consideration of the etiology of these pathologic clinical entities has been both interesting and disappointing, interesting from the ingenuity of the theories, and disappointing from the practical application by the profession. To review all of the theories would be time-consuming and without profit, therefore, the reader is referred to articles by Gage,<sup>1</sup> Fox,<sup>2</sup> and Stone,<sup>3</sup> for detailed description of the etiologic factors.

From an embryologic and clinical review the author has divided the pilonidal sinuses and cysts into four groups, as follows: Group I—(A) The simplest of all the types—the sacrococcygeal dimple, and (B) its counterpart, sacrococcygeal dimple sinus. Group II—All true pilonidal cysts and sinuses and their ramifications that are confined to the sacrococcygeal region without entering the sacral canal. Group III—All true pilonidal cysts and sinuses, multiple or single, that enter the sacral canal but are not continuous with the central canal of the cord or the subarachnoid space, but may be attached to the dura. Group IV—The rarest of all the true pilonidal cysts and sinuses, those that enter the sacral canal or pass through a defect in the sacral vertebrae and become continuous with the central canal of the spinal cord or open into the subarachnoid space. In Group IV, cerebrospinal fluid is discharged from the external opening of the sinus (Moise,<sup>4</sup> and Ripley and Thompson<sup>5</sup>).

*Pathology*—The gross pathologic manifestations of pilonidal sinus are more or less constant. There are single or multiple sinus openings which connect with cystic dilatations located subcutaneously. The cystic dilatations

are of various types. The sinuses may extend deeply toward the sacrum and a bulbous dilatation be present at its distal end. In this type the cystic dilatation is in close association with the periosteum over the sacral hiatus or extends upward over the sacrum. There may be two cystic dilatations,



FIG 1—Photograph of gross serial sections of completely removed pilonidal sinus demonstrating the cystic dilatations in the lower segments. The sinus tract is surrounded by a zone of granulation tissue.

one just beneath the dermal layer of the skin which is connected with the other cystic dilatation which is in juxtaposition with the periosteum over the sacral hiatus or the lower sacrum. When the cystic dilatation is comparatively large there are multiple sinus connections with the skin surface. Occasionally one will find a small subdermal cyst that has no sinus opening on the skin surface. In cases of the latter type there will be a very small bluish area, 1 to 2 Mm in diameter. This bluish area is due to covering over the sinus with a scant layer of epithelium. Surrounding the cysts and sinuses there is a slight tumefaction due to surrounding inflammatory reactions. If serial sections 5 cm thick are made of the removed specimen the small sinus with slight dilatation or a wide cystic dilatation can be seen (Fig 1). In rare instances the sinus tract enters the sacral canal through the sacral hiatus or through a defect in the bony covering of the canal. This sinus may then either be attached to the dura or continuous with the canal of the cord or subdural space. That part of the sinus tract entering the canal may have cystic dilatations of the lumen.

The most frequent complication of pilonidal sinus is an acute infection with abscess formation, which may be either single or multiple. The infecting organism is predominantly the *Staphylococcus*, however, the colon bacillus is not an infrequent contaminator. When the abscess is incised or ruptures spontaneously it leaves a discharging sinus. These abscesses with their secondary sinus formation are located in the majority of instances to either side of the midline. When an abscess or secondary sinus is located on either side of the midline,

it indicates that the cystic dilatation of the pilonidal sinus is located deep below the overlying skin. In this position the cystic portion is very near the periosteum of the sacrum or the sacrococcygeal junction (Fig 2). However, if the cystic portion of the sinus is located just beneath the skin surface the secondary sinus formation in the majority of instances occurs in the midline. When the cystic dilatation is just beneath the integument and an abscess develops in the cystic portion a sinus with granuloma formation invariably results (Fig 3). Therefore, the relative position of the secondary sinuses will aid in determining clinically the location of the cystic portion of the sinus. Carbuncles, though they rarely occur as a complication, may have their origin in the overlying integument or develop from secondary



FIG 2—Photograph showing a deep seated cystic dilatation of a pilonidal sinus with secondary sinus formation. There are four primary openings and one secondary sinus opening, the latter containing a granuloma.

infection of the pilonidal sinus tract. We have had only one case in which a carbuncle complicated the pilonidal sinus.

The sacral dimple seldom results in the formation of a sinus. When sinus formation occurs it then falls heir to all of the inflammatory complications that occur in true pilonidal cysts. When an abscess complicates the sacrococcygeal dimple sinus with secondary sinus formation resulting, the latter is frequently mistaken for a fistula-in-ano.

Direction of the true pilonidal sinus and its cystic counterpart is cephalad. When multiple primary sinuses are present or secondary sinuses occur, their direction in the majority of instances is straight downward to the cystic counterpart. The direction of the sacrococcygeal dimple sinus, in contradistinction to the above, is caudal.

The microscopic study of the sinus and cyst is most interesting as regards their ectodermal lining, which is practically devoid of ectodermal appendages. The epithelial lining of both the sinuses and cysts is of the stratified squamous type (Fig 4). The epithelial lining is seldom complete,

characterized by cracks, fissures, and shedded epithelium. These areas are filled in by granulation tissue. In some of the sinuses studied, desquamation of the entire epithelial lining occurred. When this condition exists, the lining is composed of granulation tissue surrounded by a wall of dense connective tissue. If abscess formation occurs in the sinus tract or its cystic portion, the resulting cavity is filled with granulation tissue, sinus formation occurs, and a granuloma results. Hair shafts and follicles are very numerous, having their origin from the ectodermal epithelial lining. The hair shafts



FIG 3—Photograph showing a pilonidal sinus secondarily infected with a granuloma presenting in one of the openings of the sinus. In this case the abscess was located in the superficial cystic dilatation of the sinus.

are immature, frequently protrude from the sinus opening, and occasionally fill the cystic dilatation of the sinus. Hair shafts and hair follicles are the only ectodermal appendages which the author has been able to demonstrate. Although others have described sebaceous and sweat glands, the author has been unable to verify these findings. Sweat glands and sebaceous glands are occasionally seen in association with the pilonidal cysts and sinuses, however, they originate from the normal overlying skin. They penetrate downward and are in juxtaposition to the cyst and sinus. This arrangement is probably responsible for the misinterpretation of the authors who have described sebaceous and sweat glands as arising from the epidermoid lining of the pilonidal sinus.

## PILONIDAL SINUS

In the sacral canal the epithelial lining is somewhat different from that which is superficial. Although the epithelial lining is of the epidermoid type, there is complete absence of hair follicles and hair shafts. The lining is a modified, stratified, squamous epithelium and is more typical of mucous membrane than skin.

All of these sinuses, both primary and secondary, reveal different degrees of inflammation, ranging from acute to chronic with concomitant fibrosis, which predominates in the chronic form. The inflammatory re-



FIG 4—Photomicrograph illustrating the stratified squamous epithelial lining of the sinus tract as well as demonstrating the presence of hair shafts and follicles. Desquamation and fissuring of the epithelial lining is clearly seen in the center. There are no sebaceous or sweat glands present.

actions are characterized by subepithelial infiltration of the various inflammatory cells (Fig 5). In the presence of abscess formation the cellular constituents are predominant of the polymorphonuclear variety, the acute reactions fading progressively as the distance from the sinus increases. Some distance from the acute reaction granulation tissue is present in varying amounts. In old cases of pilonidal sinus chronic inflammatory reaction predominates. This is characterized by extensive productive fibrosis with active granulation tissue near the lumen of the sinus. In fact, when abscesses have occurred with secondary sinus formation, the sinuses are filled with granulation tissue and the surrounding tissue is a wall of dense connective tissue. It is also common to find complete loss of epithelial lining. In this instance the lining of the sinus is granulation tissue mounted on a fibrous wall. This pathologic sequence is responsible for the granulomata seen in

association with pilonidal sinus, both primary and secondary. In the uncomplicated case, varying degrees of chronic inflammatory reactions are seen. Even in this type there are cracks and fissures of the epithelial lining, with complete deepithelialization in small areas of the tract. The inflammatory reaction in the uncomplicated case is confined in the majority of instances to the subepithelial area and is never extensive in its scope.

*Clinical Manifestations*—In the average uncomplicated case of pilonidal cyst and the sacrococcygeal dimple sinus there are four signs and no symptoms, except slight pain or discomfort occasionally experienced by the patient.

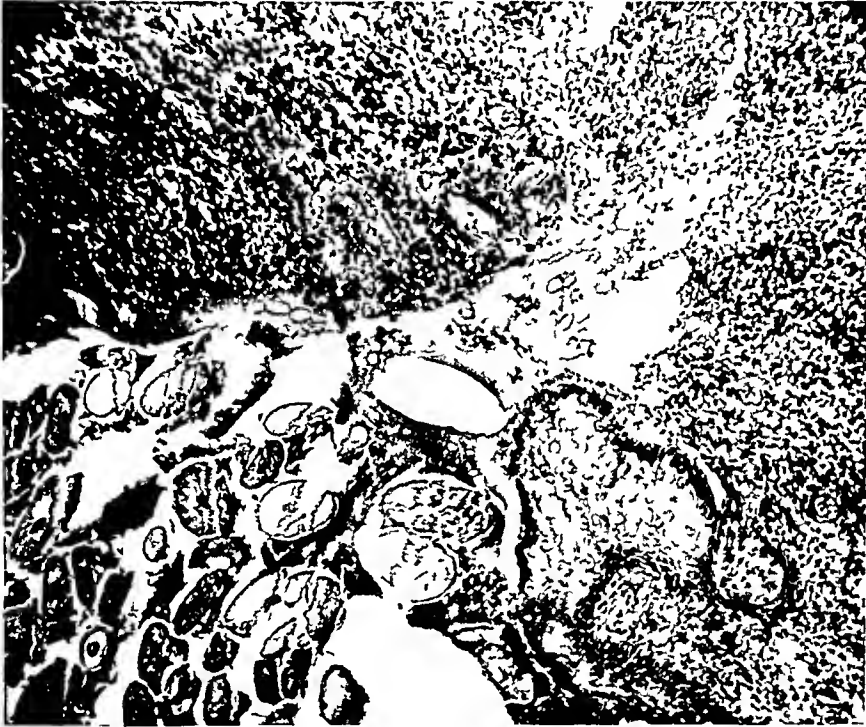


FIG. 5.—Photomicrograph demonstrating the loss of the epithelial lining with submembranous acute and chronic inflammatory reaction. Granulation tissue formation is also prominent.

The four signs are (1) Single or multiple sinus openings in the sacrococcygeal area. They vary in number from one to five, exclusive of the secondary sinus openings, however, in rare instances sinus openings are absent. When the last condition exists, there is a small palpable tumor with a small bluish area (pin point in size) in the overlying skin. This small pin point opening can be punctured easily and a probe introduced into the underlying sinus or cyst. (2) Immature hairs may or may not protrude from the mouth of the sinus. (3) A discharge may be present which keeps the median raphe moist or soils the underclothing. (4) In rare cases cerebral spinal fluid may drip from the sinus opening. Cases portraying the latter phenomena have been reported by Moise,<sup>4</sup> and Ripley and Thompson.<sup>5</sup>

The sacrococcygeal dimple is characterized by a dimpling of the integu-

ment at the site of the sacrococcygeal junction. It is of common occurrence and practically never contains hair (bald spot of Oehlecker). The dimple is saucer-shaped and is very superficial and causes the patient no discomfort. However, if the simple dimple has been converted into a sacrococcygeal dimple sinus, the same signs occur as in the true pilonidal sinus except there is no hair protruding from the mouth of the sinus which is larger than the mouth of the true pilonidal sinus.

The direction of the pilonidal sinus is cephalad, whereas the direction of the sacrococcygeal dimple sinus is always caudad. The latter is frequently misinterpreted as a sinus of the fistula-in-ano type.

The most common complication of pilonidal and sacrococcygeal dimple sinuses is infection with abscess formation which is very painful because of its location. The abscess in the majority of instances occurs on either side of the midline, seldom involving the sinus or its cystic dilatations directly, except when the cystic dilatations are just beneath the overlying skin. In the latter condition, which is not common, an abscess usually develops in the cyst. The clinical symptoms are those of an acute infection, both locally and systemically. However, the local manifestations are severe as compared to the systemic reactions, which are very mild. The abscess usually ruptures spontaneously or is incised surgically, both of which result in the formation of accessory sinuses. The author observed one patient with 27 accessory sinus openings, who still harbored his undisturbed pilonidal sinus. When the abscess is confined to a superficial cyst and ruptures or is incised, a typical granuloma results (Fig. 2). The most formidable (fortunately rare) complication that can occur is the discharge of cerebral spinal fluid from the sinus. It is always of serious import, because if secondary infection occurs within the sinus, or associated with it, meningitis invariably follows. Secondary meningitis in the majority of instances is caused by the *Staphylococcus* or *Streptococcus* and usually results in the death of the patient.

The diagnosis of pilonidal sinus and "sacrococcygeal dimple sinus" is so simple that it is frequently overlooked. The presence of sinus openings in the midline of the sacrococcygeal region immediately establishes the diagnosis of pilonidal sinus. If every patient who consults a physician could have the sacrococcygeal region routinely examined the percentage of incidence would be greatly increased. It is only by this method of examination that uncomplicated cases of pilonidal sinus can be diagnosed and operated upon before infection occurs. In all patients complaining of a discharge, pain, or discomfort in the sacrococcygeal or anal region the likelihood of a pilonidal sinus being responsible for the clinical symptoms must be considered. In all patients who have sacrogluteal sinuses or granulomata, the nates should be separated and a pilonidal sinus will usually be discovered.

The presence of an abscess in the sacrococcygeal area in the midline or on either side of the midline is indicative of a pilonidal sinus. It is, however, common for the attending physician to incise the abscess, treat it over a period of weeks, and then wonder why the sinus persists. He frequently does not



look for the pilonidal sinus. The patient then develops a secondary sinus which is likely to result in recurrent abscess formations. One patient mentioned above had 27 abscesses incised which resulted in as many sinuses. The patient still retained his pilonidal sinus.

The only difficult diagnostic problem is to determine the extent and direction of both the primary and secondary sinus tracts. The direction can be determined by simply introducing a probe into the sinus tract and noting the direction as the probe follows the sinus tract. The extent of the tract and the presence of cystic dilatation and accessory pockets can only be determined preoperatively by injecting the sinus with an opaque substance, preferably lipiodol. The sinus is then radiographed with the patient in the prone and lateral positions. The anteroposterior position determines the size and lateral projection, and the lateral position determines the extent of the sinus. The latter method is the only way by which a sinus in the sacral canal can be diagnosed.

*Treatment*—The ideal treatment of pilonidal sinus is complete surgical extirpation and primary closure of the wound. Whether this can be accomplished or not is dependent upon the presence or absence of an acute infection in or associated with the pilonidal sinus or cyst. In the presence of an acute abscess within the sinus or cyst or in juxtaposition with the deep-seated cyst, the surgical requirements are simple incision and drainage. The infection should then be actively treated until the acute manifestations have subsided. Radical extirpation of the sinus should be deferred for at least six months. In the interim the chronic infection resulting from the acute process should be minimized as completely as possible by adequate treatment of both the infected cyst and accessory sinuses. This allows the surrounding tissue an opportunity to develop a local immunity which will inhibit to a greater or lesser degree secondary infection at the time of surgical extirpation. In patients with a history of previous infection, who present at the time of their first examination multiple accessory sinuses, operation should be deferred for a week or ten days. This allows time for energetic treatment of the sinuses. The treatment consists of hot tub baths and hot moist compresses of hypertonic saline solution to the diseased area. This procedure is very important as a preoperative measure in preparing the field for operation, reduces exudation and minimizes infection following operation. No patient having secondary sinus infection subsequent to abscess formation should be operated upon without the above plan of preoperative preparation. If the above principles are adhered to, then accessory sinuses and granuloma formation are not contraindications to successful extirpation and primary closure of the wound.

The high incidence of recurrence following operation for the cure of pilonidal sinus varies greatly in different clinics. In some of the clinics the incidence of recurrence is very high, while in others very low. However, in all series reported there have been recurrences. The percentage of recurrences in the series reported by Kleckner<sup>6</sup> is probably the lowest. He

reports a collected series of 4,699 cases with an incidence of recurrence of 29 per cent. In analyzing this extensive series, he divides them into the following groups. In 4,231, the open method was used (total excision of the primary and secondary sinuses, wound packed and allowed to heal by granulation) with a recurrence in 48 cases, or 1.13 per cent, in 365 cases, total excision with primary closure of the wound with a recurrence of 33.29 per cent. In the third group there were 103 cases, with primary closure of the wound, however, due to secondary infections the wounds were opened for drainage and then allowed to heal by granulation. In this series there was an incidence of recurrence of 4.8 per cent. It is remarkable that there should be so high an incidence of recurrence of pilonidal sinus with total excision and primary closure of the wound, and a very low incidence of

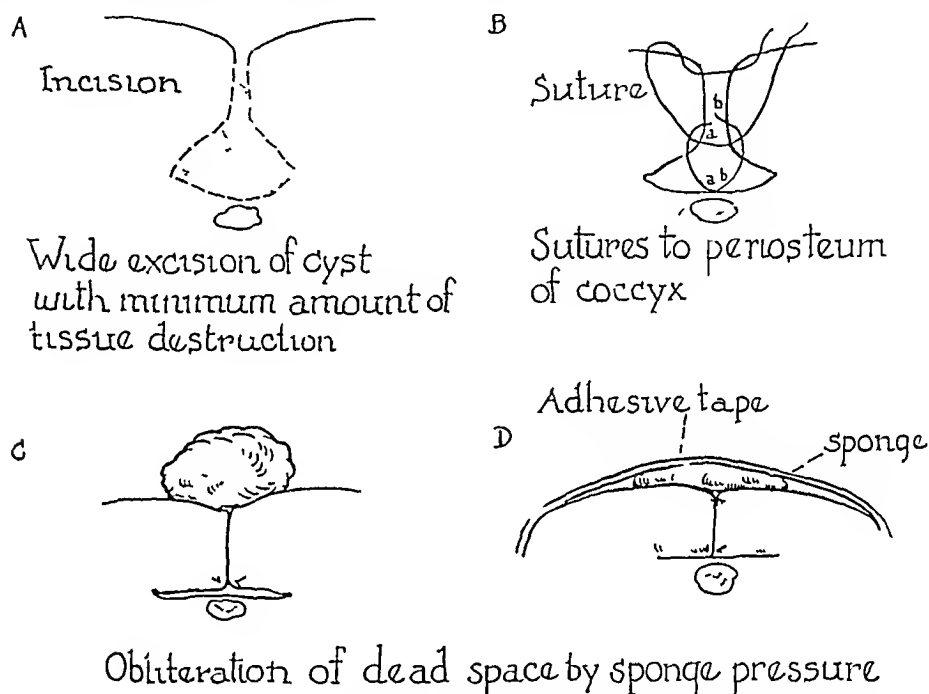


FIG. 6.—Drawing (exaggerated) illustrating the defect following the removal of a pilonidal sinus (A), the sutures used to close the defect (B), subcutaneous defect after suturing (C) and the obliteration of all dead space and approximation of all wound surfaces by "sea sponge" pressure (D).

recurrence following excision and packing the wound, allowing it to heal by open granulation. The question that immediately confronts one is, why is there such a marked difference in the incidence of recurrence in the two methods of treatment? The incidence of recurrence is dependent upon several factors which are controllable by the surgeon, which if controlled will eliminate the recurrences.

One of the most important factors responsible for recurrence is the presence of infection in both the primary sinuses and cysts as well as the secondary sinuses. When secondary sinuses are present infection is not only present but the sinus tract is partly or completely lined by epithelium. In the majority of instances the sinuses are filled with granulation tissue, with acute or subacute and chronic infection present. If the infected primary and

secondary sinuses are thoroughly treated and stained preoperatively, the entire pilonidal sinus, its cystic dilatations and secondary sinuses, can be removed safely, the wound closed by primary suture, with complete healing resulting.

The second factor and the one which is most important is the failure to obliterate dead space at the time of primary suture of the wound. After removal of the pilonidal sinus and especially those complicated by accessory sinuses, there remains a relatively large subcutaneous defect which cannot be obliterated by sutures (Fig 6). This leaves a dead space which becomes infected, granulation tissue is formed, and extensive scar tissue results. There results a cavity filled with infected granulation tissue surrounded by a wall of scar tissue. A sinus to the exterior is formed and with a persistence of symptoms or a recurrence. If this subcutaneous defect which cannot be closed with sutures could be completely obliterated and the obliteration maintained, recurrences would not occur. The subcutaneous defect or dead space can be obliterated easily and so maintained until complete healing has resulted by the simple means of sea sponge pressure. This method of approximating wound surfaces which obliterates all dead spaces until wound healing is complete is employed extensively by plastic surgeons. Therefore, this second factor, as the first, is under direct control of the surgeon.

The third factor, but probably the one of least importance, is the failure of complete removal of the epithelial lined pilonidal sinus and its accessory sinus tracts. If one will refer to the section on pathology, it is realized that the only sinus tracts likely to be incompletely removed are those that enter the sacral canal. By injecting the sinus with lipiodol followed by roentgenographic visualization the type and extent of the sinuses can be determined accurately preoperatively. Also, if the sinus tracts are deeply stained by a solution of methylene blue preoperatively, incomplete removal should not occur. The third factor is also under the control of the surgeon. Therefore, if all three factors responsible for recurrences are controllable by the surgeon, there should be a method by which complete surgical excision and primary wound closure could be accomplished, resulting in a high percentage of complete cures and a negligible incidence of recurrences.

*Preoperative Preparation*—The method used in our clinic that controls all of the above factors, which has been described elsewhere,<sup>1</sup> is as follows. When the patient is first seen he is examined for the presence of infection in the pilonidal sinus. If infection is present either in the primary sinus or secondary sinus or both, the infection is vigorously treated until the infecting organisms have been sufficiently reduced to justify surgical excision. No instrumentation or injection should be undertaken until all infection has subsided. Then the sinus is probed to determine its direction and extent. This is supplemented by anterior, posterior, and lateral roentgenograms of the sacrococcygeal region following the introduction of lipiodol into the sinus and its ramifications. Having determined by the above method the type and

extent of the pilonidal sinus, the next and most important procedure is to thoroughly stain the sinus, its cystic dilatation, as well as its accessory sinuses. This staining is accomplished as follows. Five days before the operation the pilonidal sinus is injected with a solution of methylene blue under slight pressure. This injection is again repeated on the fourth and third preoperative days, respectively. Two days now elapse before the operation. This allows the sinus tract to "dry out," leaving the walls of the cyst and sinus deeply stained a bluish color. This method of staining the sinuses confines the stain to the sinus tract and prevents staining of the surrounding tissue at operation. The surgeon can easily distinguish the diseased from the normal tissue, whereas, if the sinus is injected at the time of operation, the dye solution spills into the operative field. The dye solution immediately stains

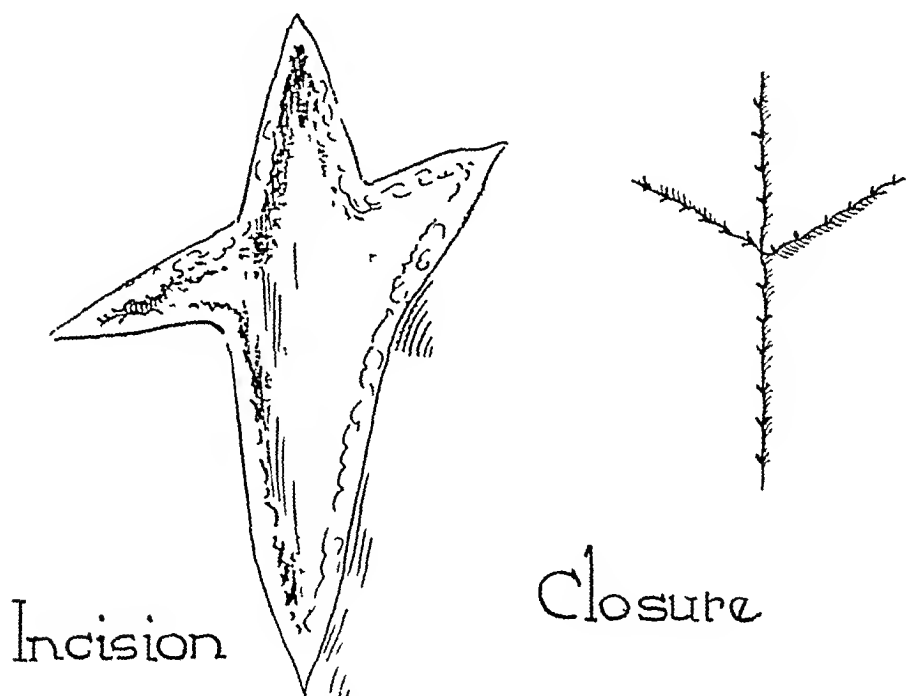


FIG. 7.—Drawing illustrating the method of excising the primary pilonidal sinus and the lateral or secondary sinuses, and the wound after closure.

all exposed tissue and the normal and abnormal are of the same color and cannot be distinguished from each other. By the above method failure to remove completely all of the sinus tract is eliminated.

*Operative Procedure*—After the sinus tract has been defined and stained the operation proceeds as follows. With the patient in the prone position, a pillow is placed beneath the pubis and adhesive straps are applied to the buttocks on either side and fastened to the table. The adhesive straps separate the buttocks and act as retractors. In the noninfected type an incision can be made directly into the sinus, the sinus easily dissected from the surrounding tissue with a minimum loss of tissue, and the resulting wound can be easily closed by suture. However, in the majority of instances secondary sinuses are present and necessitate a more extensive dissection, which can be accomplished also with a minimum loss of tissue. An elliptical

incision is made around the primary sinus opening and extends down to the periosteum over the sacrum or sacrococcygeal region (Fig 7) If necessary a probe can be easily introduced from the mouth of the accessory sinus through the tract into the open wound This will facilitate the dissection of the secondary sinus tracts The wound is thoroughly inspected and remnants of the sinus tract searched for All bleeding points are now ligated with fine silk and the wound closed by retention sutures of silk or silkworm gut After closure of the wound edges an unobliterated dead space is always present at the bottom of the wound due to the nature of the wound (Fig 6) If this dead space is not obliterated a recurrence will take place Therefore, complete apposition of all wound surfaces and obliteration of all dead spaces is secured by pressure over the wound This pressure must be constant and distributed evenly, and is obtained only by the use of sea sponges (Fig 6) This pressure dressing is left undisturbed for a period of 10 to 12 days If, however, it becomes necessary to change the dressing, the sponge pressure must be repeated In reapplying the sponge pressure, one should never use the same sponges, because they become molded to the parts and have lost their resiliency, having been applied while wet Therefore, a fresh, sterile, moist sponge must always be used in redressing the wound

The above method has been employed in 42 cases of pilonidal sinus, without a single recurrence There have been nine cases of skin infection with good healing, and one case that developed a deep infection which necessitated wound opening This case healed by open granulation

Dr L H Strug<sup>7</sup> has used the same method in 54 cases with primary healing of the wound in 52 One case had a Streptococcal gangrene of the skin, and the other had an accumulation of serum in the wound, which was aspirated three times before healing was completed There have been no recurrences in Doctor Strug's series

#### CONCLUSIONS

Pilonidal sinuses and cysts are of common occurrence They are derived from that part of the caudal end of the medullary canal located in the tail anlage They are divisible into four groups (1) Sacrococcygeal dimple and sacrococcygeal dimple sinus, (2) true pilonidal sinus, confined to the subcutaneous tissue, (3) true pilonidal sinus extending into the sacral canal, and (4) true pilonidal sinuses which are continuous with the subarachnoid space and canal of the spinal cord

A method is described by which surgical excision and primary suture will give a high percentage of cures and a low incidence of recurrence

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# GAS GANGRENE FOLLOWING THERAPEUTIC INJECTIONS

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Gas gangrene, developing as the result of subcutaneous or intramuscular medicinal injections, has been reported in the foreign literature in numerous papers, but, to date, there has appeared only one article in the American literature dealing with this condition. In 1936, Tenopyr and Shafiroff<sup>59</sup> reported three cases of gas gangrene following hypodermoclysis. Two of these patients died, and one recovered.

The first cases, of which the author was able to find any record, were reported by Brieger and Ehrlich,<sup>9</sup> in 1883. The first was that of a woman, age 26, who was extremely ill with typhoid fever. She had received a subcutaneous injection of moschus tincture into the right thigh. On the second day thereafter, typical symptoms of gas gangrene developed at the site of the injection, with swelling, pain, crepitation and discoloration. The patient died the following day without surgical intervention. The second case was that of a woman, age 32, also suffering from typhoid fever. She had received injections of ether and oil into the thigh. On the second day following the injections, the typical clinical findings of gas gangrene developed in the injected thigh, and on the fourth day the patient died without surgical intervention. The bacillus of malignant edema was found in both cases.

The second article dealing with this subject was that of Fraenkel,<sup>16</sup> in 1893, who reported two cases. One of these cases followed the injection of camphor, oil and ether, and the other of morphine. Other instances have been reported at irregular intervals since that time, until the later years of the World War, when the incidence of reported cases increased sharply. Seventy per cent of reported cases have appeared in the literature during the last ten years. In 1933, Junghans<sup>27</sup> collected 60 cases. Twenty-five additional cases have been found in the literature, and one case of our own is added, making a total of 86 cases of gas gangrene following the injection of medicaments.

**Case Report**—W. P., colored, male, age 63, was admitted to the Bryn Mawr Hospital April 3, 1936. A tentative diagnosis of partial intestinal obstruction was made at the time of admission, and during the next two days the patient received several intravenous injections of glucose in normal saline solution, into the veins of both arms. On April 5, an exploratory celiotomy was performed through a lower right rectus incision. A loop of the lower ileum was found to be strangulated in the right inguinal canal. The bowel was released, and after its viability had been determined, it was replaced in the abdomen. The internal abdominal ring was closed from within, and the abdominal wound sutured.

**Postoperative Course**—Before and after operation, the patient received injections of morphia into the arm. During the afternoon and night of the third postoperative day, the

patient received one injection of pitressin, and five injections of digalen. One of the injections of digalen was given into the right thigh. The other injections were given into the arms. Twenty-four hours after receiving the injection into the thigh, the patient complained of pain at the site of the injection. Upon examination, the thigh was swollen, tender and hot, these signs being most marked at the site of the injection. No crepitation was elicited at this time, and hot, wet dressings were applied. During the course of the next 12 hours, the patient's temperature rose from normal to 102.3° F. The local signs in the thigh became more marked, and crepitation was elicited.

Under local anesthesia, wide incisions were made into the infected thigh, and anti-perfringens serum was administered, both into the tissues about the wound, and intravenously. The tissues were found to be distended with gas, and necrotic.

The patient expired six hours following this operation. Cultures of the infected tissues and of the skin of the unaffected thigh showed gram-positive rods which produced gas under anaerobic conditions. Culture of the digalen solution was sterile, but the syringe and needle were not cultured.

Seventy-six of the 86 cases reported, terminated in death, a mortality of 88.4 per cent. This figure is in marked contrast to the mortality of 49.7 per cent in 607 collected cases of gas gangrene following various injuries (Miller<sup>40</sup>).

The sites of injections were stated in 59 cases reported in the literature, and of these, 55 were in one or both thighs, the buttocks, or abdominal wall. Table I gives the sites of injection, and Table II shows the wide variety of drugs injected.

TABLE I  
SITES OF INJECTIONS

One thigh	45
Both thighs	3
(both injected and both infected)	
Buttock and arm	3
(both injected and both infected)	
Thigh and arm	2
(both injected and both infected)	
Breast	2
Arm	2
Abdominal wall	1
Buttock	1

In nearly all cases reported, drugs, syringes, needles and solutions were cultured. A preparation of caffeine and digitoxin was found to contain gas organisms by Heuss.<sup>25</sup> Nauwerck<sup>42</sup> found gas bacilli in a preparation of caffeine sodium salicylate solution. Semenoff<sup>37</sup> and Anschutz<sup>1</sup> were able to culture gas bacilli from the needles used in their cases. These needles had been preserved in 96 per cent alcohol. Dimtza<sup>12</sup> found gas bacilli in one syringe, one needle, and in four files of the type used in breaking glass ampules. In all other instances in which studies were carried out, the drugs, solutions, syringes and needles were found to be sterile.

The patients to whom the injections were given suffered from a wide



TABLE II  
MEDICAMENTS INJECTED

Caffeine	19
Adrenalin	11
Saline solution	9
Camphor	7
Quinine	5
Hackel's anti-asthmatic serum	5
Morphine	3
Digalen	3
Asthmalylin	2
Moschus tincture	2
Novocain	2
Ether and oil	2
Digatol	1
Ommidine	1
Afenil	1
Calcium	1
Digipurate	1
Scopolamine	1

variety of diseases. Almost all of them were severely ill. The most frequent diseases were pneumonia, typhoid and malaria.

The time elapsing between the injection of the drug and the appearance of the clinical symptoms of gas gangrene was difficult to determine in most instances. This was true because the patients had usually received several injections over a period of several days. In 21 cases, we can say with certainty that clinical symptoms appeared between ten and 36 hours following the contaminated injections.

The time elapsing between the appearance of the clinical symptoms and the time of death could be accurately determined in 45 cases (Table III).

TABLE III  
INTERVAL BETWEEN APPEAR-  
ANCE OF CLINICAL SYMPTOMS  
AND DEATH

17 died during the first day
21 died during the second day
3 died during the third day
1 died during the fourth day
2 died during the sixth day
1 died during the seventh day

No attempt has been made in this paper to deal with the bacteriology, clinical course or treatment of gas gangrene. Attention is drawn to the facts that gas gangrene can and does occur after the hypodermic or intramuscular injection of medicinal agents, that the mortality is very high, *ie.*, above 88 per cent, and that injections in the thigh are much more likely to be followed by gas gangrene than injections elsewhere in the body. The relatively high mortality in the cases in this series is possibly due to the fact

that almost all of the patients were severely ill before the contaminated injections were given. It is considered highly significant that 55 out of 59 contaminated injections were given into areas of the body surface which might easily be soiled by fecal material. For this reason, it is recommended that such areas—namely, the thighs, buttocks, and abdominal wall—be avoided when giving hypodermic or intramuscular injections. If these areas must be used, then the skin should be carefully sterilized, instead of receiving the perfunctory dab with an alcohol sponge, which is customary in most hospitals.

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# THE EFFECT OF CONSTANT GASTRIC SUCTION ON THE ACID-BASE EQUILIBRIUM OF THE BODY\*

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WESTERMAN,<sup>1</sup> in 1910, introduced and popularized the use of the stomach tube for the postoperative treatment of peritonitis. This discovery was as far reaching in its effects and its benefits to the surgical patient as the stethoscope has been to the medical patient. Levine,<sup>2</sup> in 1921, introduced his duodenal catheter which was a great improvement over the instrument of Westerman, especially so in its ease of application and usefulness. In 1925,<sup>3</sup> Ward<sup>4</sup> first presented an apparatus for producing constant gastric suction, and, in 1930, described remarkably beneficial results with the use of this instrument in acute dilatation of the stomach. He also advocated its use in paralytic ileus, intestinal obstruction, and postoperative vomiting. Many modifications of Ward's apparatus were described during the following years,<sup>5, 6, 7, 8</sup> the principal one of which was that of Wangensteen,<sup>9, 10, 11, 12, 13, 14</sup> first described completely in 1933, and which immediately became universally employed.

The Wangensteen apparatus (Fig 1) has been used in the State of Wisconsin General Hospital since its first description in 1933 to the present time, with minor modifications. It consists essentially of a closed system containing water which creates a constant negative pressure on an inlying Levine duodenal tube. The use of this apparatus postoperatively has reduced the mortality and morbidity of all patients in whom upper abdominal surgery has been performed. It has also been life saving in cases of intestinal obstruction when used alone, or in conjunction with operative measures. Many authors<sup>15</sup> consider this to be the greatest advance in the care of surgical patients recorded during the past decade.

During the past two years, some disadvantages of the employment of constant gastric suction have been noted. Taylor<sup>16</sup> has reported two cases of alkalosis, resulting in death in one instance, following its use.

*The Acid-Base Equilibrium of the Body*—This is a finely balanced mechanism which remains remarkably constant unless seriously interfered with. Gamble's<sup>17</sup> description of this mechanism, in 1924, is probably the best and most readily understood outline of this difficult subject. He considered the important basic constituent of all body fluids to be sodium and the important acid constituents of all body fluids to be the chlorides and carbonic acid.

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\* Thesis submitted to the Faculty of the Graduate School of Medicine of the University of Pennsylvania, in partial fulfillment of the requirements for the degree of Master of Medical Science (M Sc [Med]) for graduate work in surgery. Submitted for publication May 4, 1938.

Figure 2 graphically depicts Gamble's concept of this equilibrium. He also showed that a loss of the sodium ion from the body is the essential factor in rapid dehydration, and that vomiting causes more of a loss of the chloride ion than of the sodium ion, therefore, alkalosis ensues, the coincidental loss of

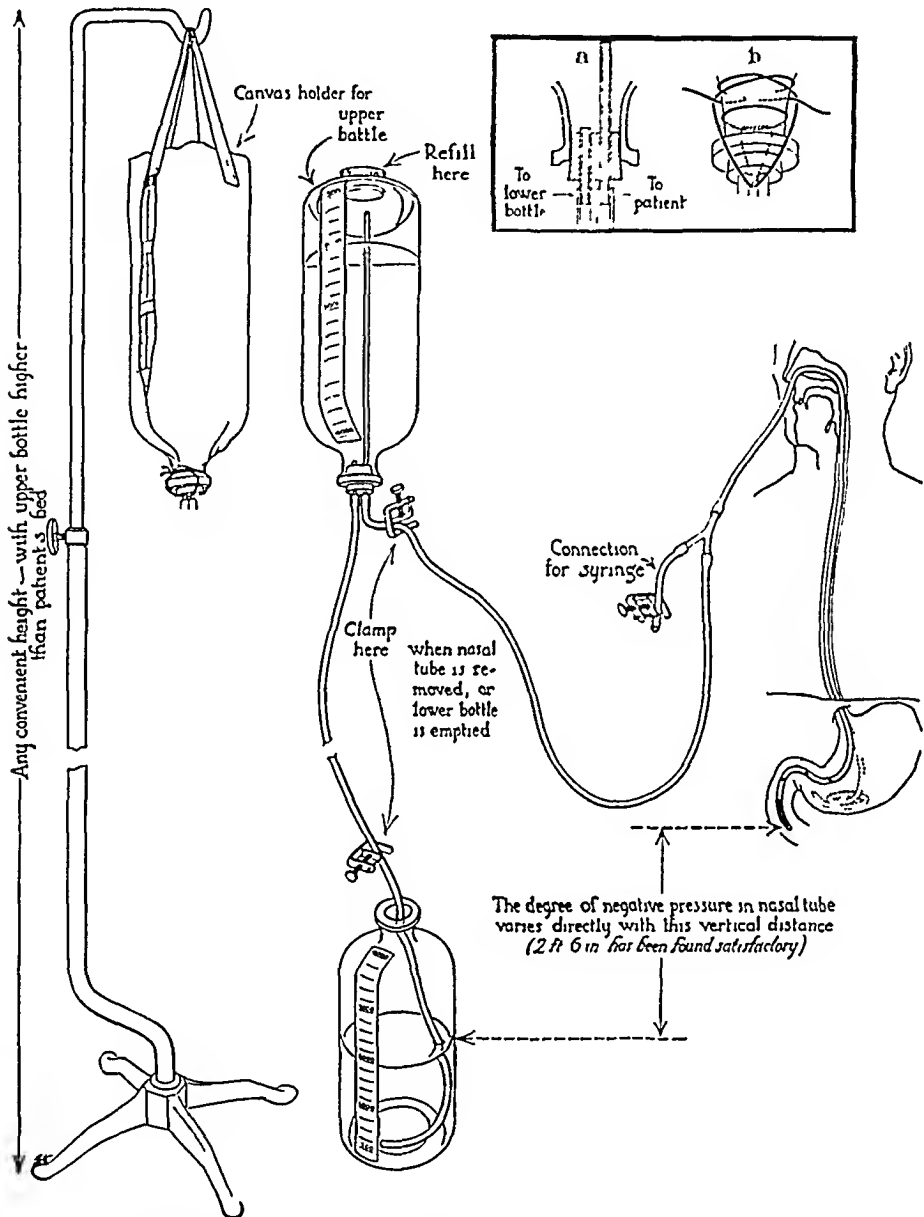


FIG. 1.—Illustrating the apparatus as originally devised by Doctor Wangensteen<sup>6</sup> employed to effect continuous gastric or duodenal suction (Reproduced from Minn Med 16 96 1933)

sodium, however, causes the dehydration. Alkalosis was reduced somewhat by an increase in carbonic acid to balance the loss of chlorides. With the kidneys in good condition and functioning normally, a moderate increase of either an acid or an alkali radical will be compensated for by having the excess

excreted in the urine, and, in the case of carbonic acid, the lungs aid in its excretion as carbon dioxide

*Method of Determination*—The best means of estimating the relative acid or basic properties of the human organism are by blood determinations of the carbon dioxide combining power and the blood chloride. The  $\text{CO}_2$  combining power is considered normal anywhere between 40 and 60 volumes per cent, and chloride values are considered normal between 400 and 600 mg per 100 cc

*Chemical Changes Produced by Depletion of Gastric Juice*—These have been studied by MacCallum and coworkers,<sup>18</sup> Hadon and Oll,<sup>19</sup> Gamble and Ross,<sup>17</sup> Dragstedt and Ellis,<sup>20</sup> and Hastings *et al*.<sup>21</sup> They all agree that the continued loss of gastric juice leads to dehydration, alkalosis and death, and have produced experimental evidence to support those views. There are, however, no data available showing the chemical changes produced in the blood by the clinical application of the Wangensteen apparatus

For purposes of this study, 50 ward cases, in which the Wangensteen apparatus was employed, were followed. These cases were chosen at random and included, for the most part, patients who had had upper abdominal surgery performed or who were suffering from some form of intestinal obstruction, either pre- or postoperatively. Daily estimations were made of the blood chlorides and  $\text{CO}_2$  combining power. The intake and output of all fluids, both oral and parenteral, were recorded, and the quantitative estimation of chlorides removed by the gastric suction determined. Retention tests were also performed daily, to determine whether or not the obstruction in the gastro-intestinal tract, due either to operative trauma with edema or an actual obstruction, had become patent and was permitting some of the gastric juice to pass into the intestines

*Results*—In the present investigation it was found that from one to four liters of fluid could be removed daily from the stomach by the Wangensteen apparatus and, along with this, one to 14 Gm of chlorides. The amount of chlorides removed had no relationship to the acidity of the stomach, regardless of whether a hyperchlorhydria or an achlorhydria was present previously. This agrees with the observations of Cohen,<sup>22</sup> the result of animal experimentation. The administration of large quantities of fluid orally, producing a lavage action on the stomach, was the principal factor in causing an increase in gastric secretion, in both our observations and in those of others.<sup>9, 16</sup> The amount of

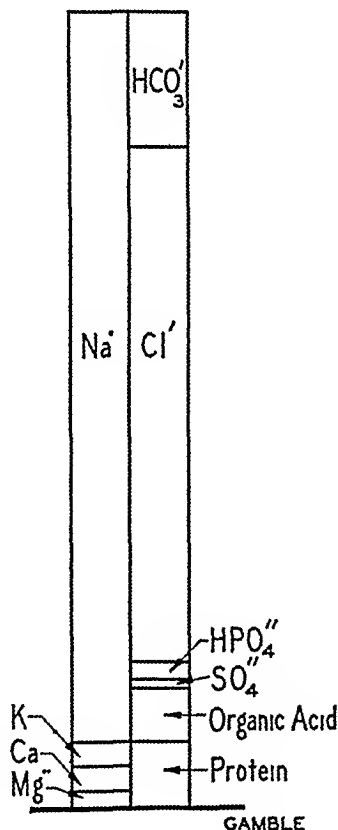
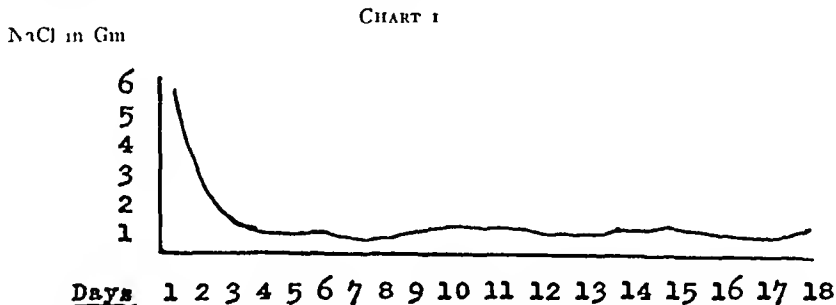


FIG. 2—Graphic representation of Gamble's<sup>17</sup> concept of the acid base equilibrium of the body. (Reproduced from *J Clin Invest*, 1, 403, 1924-1925.)

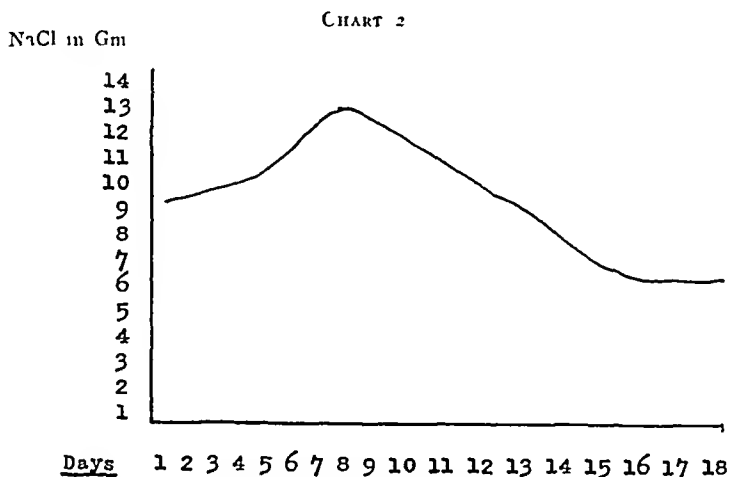
parenteral fluids, especially so in the case of saline solution, also played a prominent rôle<sup>20</sup>

Chart 1 represents a composite graph of the chloride loss in the usual postoperative cases in which the Wangenstein apparatus was used for only a few days. The gastric tube in this type of case was removed as soon as it could be demonstrated, by a retention test,\* that the pyloric or operative stoma had become patent, was functioning, and permitted gastric juice to pass



Average secretion of NaCl following operation and application of constant gastric suction

into the intestines. It will be noted that, on the first day postoperatively, about 6 Gm of chlorides were removed by the suction apparatus, and this rapidly tapered down to 1 Gm, coincident with the opening of the pyloric or operative stoma, as soon as the edema resulting from the operative trauma had subsided, which allowed some of the chlorides in the stomach to pass into the intestines.



Cases in which stoma does not open

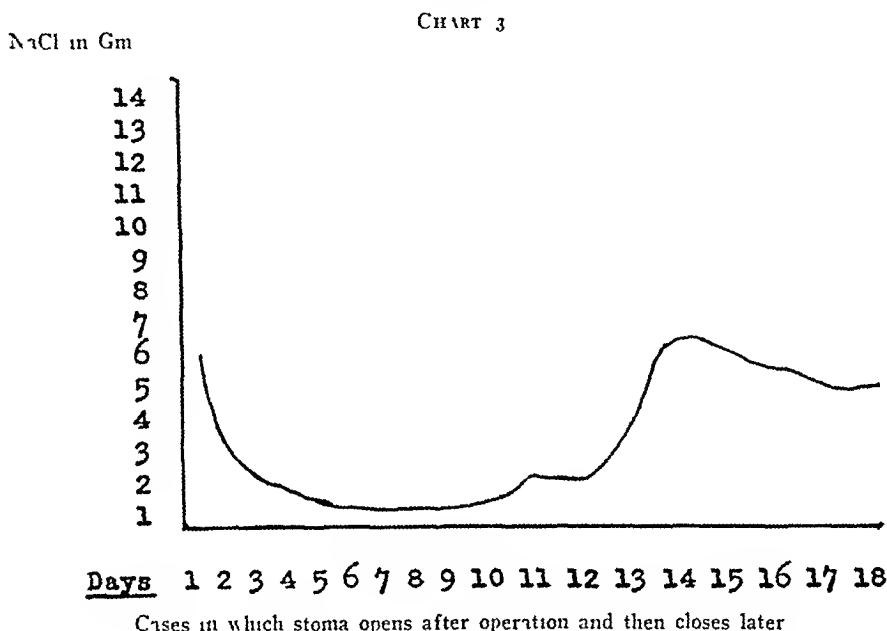
Chart 2 represents a composite graph of the chloride loss of those cases in which the stoma failed to open in the usual time. In these cases the chlorides

\* A retention test is performed by emptying the stomach through the inlying gastric tube and then placing 200 cc of water into the stomach and clamping off the tube. At the end of two hours the water remaining in the stomach is siphoned off and measured. If the amount obtained is less than 30 cc, this indicates to us that the pyloric or operative stoma is open and material from the stomach is passing into the intestines.

were lost in the amount of 6 to 14 Gm daily, and had to be supplied parenterally to prevent changes occurring in the chemical balance of the blood

Chart 3 represents a composite graph of the chloride loss of those cases in which the stoma opens for a time and closes later because of a breakdown of the anastomosis, or obstruction due to infection, adhesions, *etc*. In this instance the usual drop and leveling off of the curve occurs, to be followed later, when the obstruction intervenes, by a rapid rise

Numerous other factors that influence the amount of chlorides lost were also appreciated. As previously mentioned, the amount of fluids given orally and parenterally was the most important factor in causing an increase in chloride secretion in the stomach, as determined by their subsequent removal



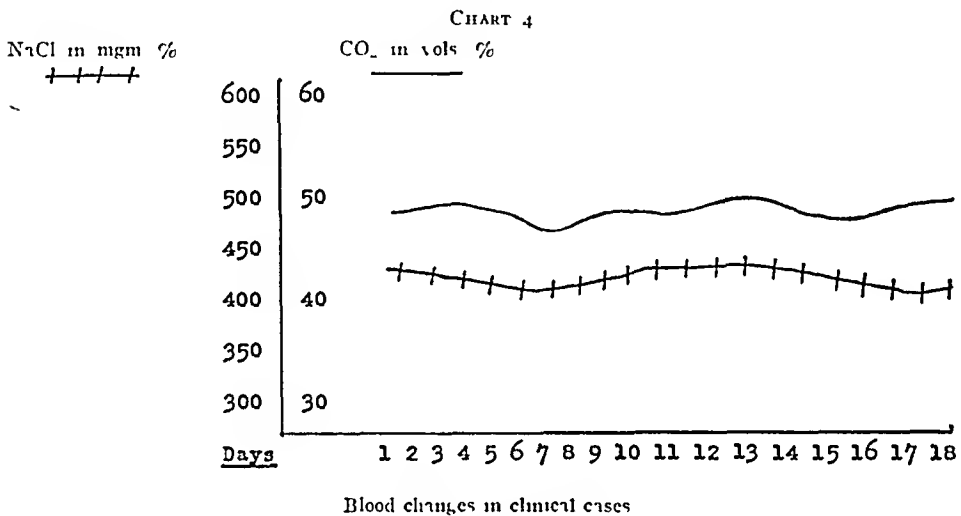
by the Wangensteen apparatus. Psychic stimulation also seemed to play a minor rôle, as did also drug therapy. When large sections of the stomach were resected, the chloride secretion was always found to be somewhat lessened in these cases. The development of peritonitis, pneumonia, or starvation, all of which have a tendency to produce acidosis, slowed down the loss of chlorides and consequent tendency toward alkalosis.

The blood changes in our clinical cases, followed by  $\text{CO}_2$  and chloride estimations, were unusually constant and within normal limits. Even though parenteral saline solution was withheld from several patients for periods of four days to one week, no significant change in their blood chemistry occurred. This would seem to indicate that, as long as minimal amounts of gastric juice are able to pass into the intestines and be absorbed, the acid-base equilibrium will be maintained and that, in the presence of a complete block at the operative or pyloric stoma, the body stores of chlorides could be expected to prevent any changes in the blood chemistry for several days. We did not have the courage to permit any of our cases to develop alkalosis, by withholding parenteral administration of saline solution for a sufficiently long period, as it



was considered that this phenomenon could be adequately demonstrated by animal experimentation. However, the two cases reported by Taylor and several personal communications from other observers are ample evidence of what may, and will, take place from too great a loss of chlorides. Chart 4 represents a composite graph of the blood changes encountered in our cases.

In animal experimentation on dogs, we created gastric fistulae, to study the effect of the loss of chlorides on their acid-base equilibrium, as the nearest approach to what we were dealing with clinically. This was only corroborative of the observations of previous workers<sup>17 18 19 20 21</sup>. We did, however, find that alkalosis could be produced only by the total loss of gastric secretion and



that, if the pylorus were not tied off or blocked artificially, the changes produced in the blood chemistry would be insignificant. These findings have worked in very nicely with the observations on the opening and closing of the stoma in our clinical cases with the subsequent loss of minimal or very great amounts of chlorides.

In one dog, we created a gastric fistula and followed his blood changes for 22 days, without noting any marked deviations. A second operation was then performed in which the pyloric sphincter was tied off and within a few days the chlorides dropped to values around 100 and the CO<sub>2</sub> rose to values over 100, with the production of alkalosis and death. No saline solution was administered parenterally to combat this.

The patients showed no edema following the administration of moderate amounts of saline solution, but in several of the experimental animals, to which we administered huge amounts of saline solution, this phenomenon was noted. Coonse<sup>23</sup> and others<sup>24</sup> have previously noted this effect. These observers attribute the edema to elevation of the blood chlorides and postulate that, when patients with kidney insufficiency are given doses of sodium chloride of 15 to 20 Gm daily, edema will occur. Helwig,<sup>25</sup> *et al*, report a case in which an overzealous nurse administered nine liters of tap water in 24 hours, by proctoclysis, causing the death of the patient soon after in convulsions.

Two of our cases, that had had an indwelling gastric tube for more than ten days, came to autopsy, and, on examination, showed a moderate amount of ulceration of the nasopharynx and esophagus in each. These changes were unquestionably due to a pressure necrosis from the gastric tube.

#### CONCLUSIONS

(1) The Wangensteen apparatus is a definite aid in the postoperative treatment of many patients, but has certain limitations and dangers.

(2) The production of alkalosis and death by constant gastric suction, used under ordinary circumstances, is almost impossible to attain unless there is a complete obstruction at the pylorus, or operative stoma.

(3) With obstruction at the pylorus or operative stoma, alkalosis will be produced within five to eight days, unless sufficient parenteral saline solution is administered to combat it.

(4) Excessive amount of saline solution, administered parenterally, will produce edema of the tissues especially so in the presence of damaged kidneys.

(5) Cases requiring constant gastric suction for periods extending over ten days are apt to develop necrosis and ulceration of the nasopharynx and esophagus.

Acknowledgment and appreciation is made of the help and constructive criticism of Dr. Erwin R. Schmidt in the preparation of this paper and also the assistance of Dr. Marion Kimble in making the necessary chemical analyses.

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# MEMOIR

FREDERIC JAY COTTON

1869-1938

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IN THE death of Dr. Frederic J. Cotton the surgical profession of America lost a member of great and varied talents, industry, and ability who had greatly impressed his personality upon the surgical world, and had taken his place among the leaders of our profession.

He was born September 24, 1869, the son of Joseph P. and Isabella C. Cotton. His father was a civil engineer, and in his office he may have developed that remarkable talent for drawing that stood him in such good stead during his professional career.

He was educated at the Rogers High School in Newport, Rhode Island, was graduated from Harvard College in 1890, and from the Harvard Medical School in 1894, receiving the degree of A.M. at the same time as the M.D. degree. The A.M. degree was at that time given to graduates of the medical school who ranked high in the newly begun four-year course. He then studied bacteriology in New York and spent two years in Vienna, where, in addition to a thorough knowledge of bacteriology, he required a knowledge of French and German which later aided him greatly in his earlier years in Boston, where he collaborated in Bradford's and Lovett's book on Orthopedic Surgery. He established the laboratory of bacteriology at the Infants Hospital, and did pioneer work in the same subject at the Massachusetts General and the Children's Hospitals. He served as surgeon in the Spanish War, and his knowledge of bacteriology and of civil engineering both contributed to make his work in sanitation especially efficient.

He served for four years on the staff of the Children's Hospital during the early years of its organization, but on his resignation in 1902, was appointed surgeon to outpatients at the City Hospital where he served for 30 years, rising through all the grades to be Surgeon-in-Chief and President of the staff in 1891, when he reached the age limit and resigned. His training at the Children's Hospital had given him special interest in diseases and injuries of the bones and joints, in which subject there is a tremendous opportunity for study at the City Hospital where the street accidents of a great city are collected under one roof. He distinguished himself in the treatment of fractures and dislocations. He had named for him Cotton's fracture of the ankle (Pott's fracture with backward dislocation of the lower fragment) which he minutely described and for which he devised an effective treatment. He was particularly active in the study and treatment of fractures of the neck of the femur, which he managed by employing his own method of impaction with a mallet, and immobilization with plaster in an abducted position. He devised and practiced many ingenious methods to aid in the treatment of fractures and dislocations. As the work of the hospital expanded it was found necessary to organize a special bone and joint service. This was perfected by Doctor

Cotton He was made chief of the service and held this position as long as he was connected with the hospital. He was for four years, from 1908 to 1912, Chief Surgeon at the Beth Israel Hospital, and Professor of Surgery in the Tufts Medical School. He was always interested in teaching, particularly graduate teaching, and was for a time Assistant in Surgery at the Harvard Medical School and afterward Lecturer in the Graduate School. He acted as consultant to many hospitals throughout New England. For several years he served as chairman of the Medical Advisory Committee of the Massachusetts Industrial Accident Board. He was clear and impressive in his language and therefore an excellent teacher, so that his ingenious and clever methods became widely known and used by the profession.

He contributed very extensively to the literature on fractures and dislocations, collaborating, as has been noted, in Bradford's and Lovett's book on Orthopedic Surgery, and Scudder's Treatment of Fractures. In 1910, his own book, Dislocations and Joint Fractures, was published by W. B. Saunders and Co. This proved very popular, and a second revised edition was published in 1924. His ability as an artist greatly enhanced the clarity and charm of his surgical writings. He wrote the division on Fractures in Lewis' System of Surgery.

He was one of the Founders of the American College of Surgeons, was a member of its first Board of Regents, and for many years served as a member of the Committee on Fractures. He served on the Board of Governors from 1925 to 1938, and at the same time was a member of the Committee on Industrial Medicine and Traumatic Surgery. For several years he served as chairman of the Massachusetts Credentials Committee. He had been selected by the Fracture Committee to give the Fracture Oration at the New York Meeting of the College in 1938. He was a member of the American Surgical Association, the New England Surgical Society, the Boston Surgical Society, the American Academy of Orthopedic Surgeons, the American Medical Association, the Massachusetts Medical Society and the Boston Orthopedic Club, of which he was at one time president.

In 1917, Doctor Cotton enlisted in the United States Army and served with distinction with the rank of Major. Previous to this he was a member of the General Medical Board of the Council of National Defence, under the chairmanship of Dr. Franklin H. Martin. He was active in reconstruction work both during and after the war, and led in the organization of the Parker Hill Hospital, of which he was Surgeon in Charge. In the summer of 1918, he was Surgeon-in-Chief at the Walter Reed Hospital. He was later Consultant to the Public Health Service and the Veterans' Bureau. Doctor Cotton was a regular attendant at medical meetings. His discussions were clear and accurate, and generally contributed something to the subject, and were illustrated by drawings on the blackboard. His many papers were original in material and clear in presentation. He was a natural teacher, and became the friend and advisor of many younger men, who regarded him as their authority on surgery of the bones and joints.

Doctor Cotton was married to Jane Baldwin of Maryland, who survives him, with a daughter, Jean, and two grandchildren

He was an enthusiastic sportsman and made regular trips to Canadian waters in successful search for trout and salmon. His chief hobby was sculpture, and his bronzes were really excellent enough to put him in the very first rank among amateurs. He was influential in founding the "hobby exhibit" for the members of the Massachusetts Medical Society, certainly an incitement to the better use of leisure.

He had a long, active and varied career, and filled an important place in many departments of our profession. He was active in his work up to the very day of his death at his home in Boston on April 14, 1938, and so was spared a lingering illness and inactivity. He will be missed by many friends, and his loss will be felt by the entire profession.

FRED B. LUND

## TO THE EDITORS OF THE ANNALS OF SURGERY

A FEW days ago I received a letter from Dr Alfred J Brown of Omaha, Nebraska, enclosing a reprint entitled *The Treatment of Colles' Fracture Considered from the Standpoint of Muscle Physiology*, from the *American Journal of Surgery* of May, 1917, 21 years ago

The method of reduction that he employed was different from the one I described in the *ANNALS OF SURGERY* for July, 1938 His conclusions followed a study of muscle pull while mine were reached after analyzing the results of treatment in 125 cases In both instances complete supination seemed to be the logical position for immobilization Figure 8 in his reprint also shows the wrist flexed and in ulnar adduction although the flexion is not mentioned in the body of the paper His letter speaks of "Supination, slight flexion and ulnar adduction"

I wish to give to Doctor Brown the credit for priority in advocating supination (unless someone else can trace it back to Hippocrates), for Buxton's paper was published in 1926, five years later

I studied the abstracts of 150 articles on Colles' fracture that had been prepared at my request but failed to see this splendid paper by Doctor Brown I hope that you will publish this letter in the *ANNALS OF SURGERY* and that this added publicity may further stimulate the use of this better method for immobilizing Colles' fracture

HENRY F GRAHAM

December 13, 1938

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### ERRATA

In the Book Review of *Thoracic Surgery*, appearing in the *ANNALS OF SURGERY*, 109, 159-160, January, 1939, Dr Sauerbruch's name was misspelled and the publishers were "Baltimore, Wm Wood and Company", and not Philadelphia, J B Lippincott Company The title should therefore read

### BOOK REVIEW

*THORACIC SURGERY* By Ferdinand Sauerbruch, M D, and Laurence O'Shaughnessy, M D, F R C S A William Wood Book by the Williams & Wilkins Company, Baltimore, 1938

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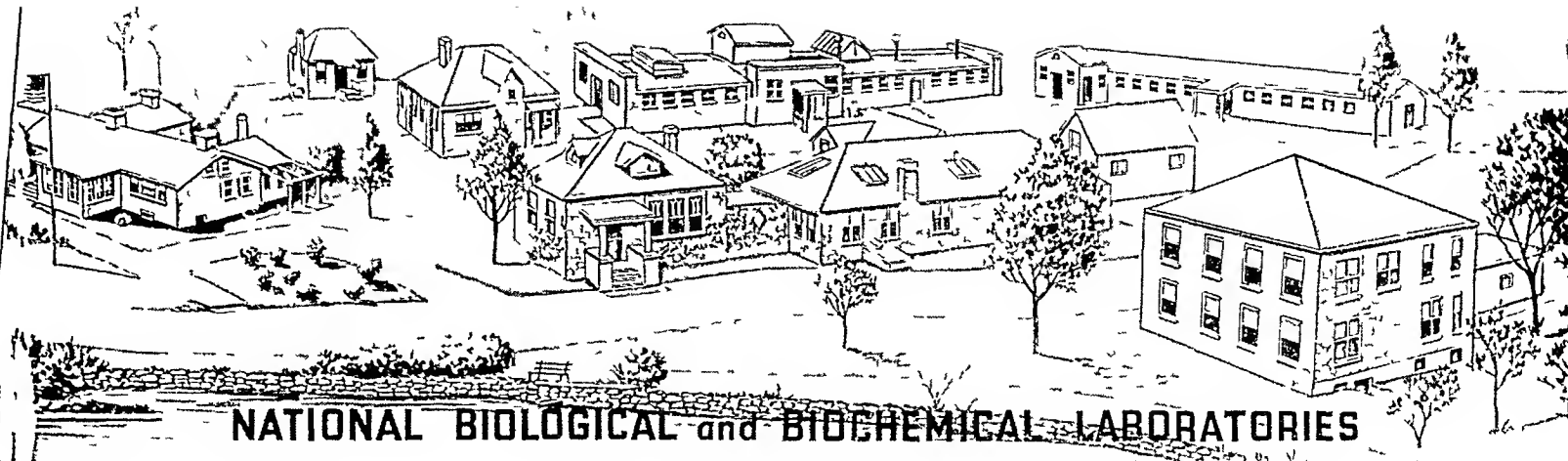
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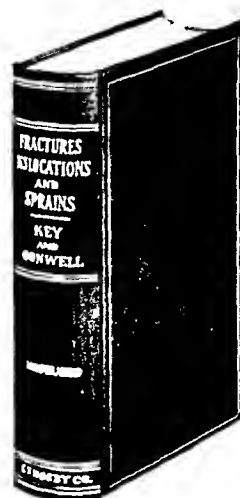
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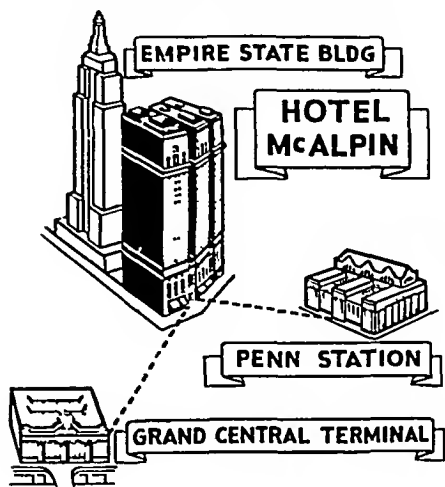
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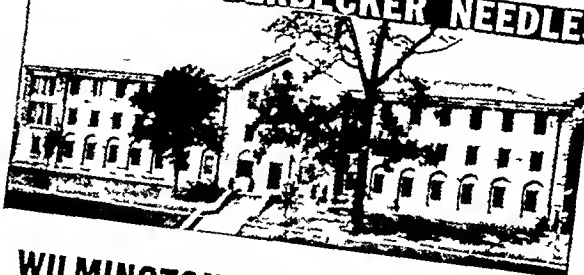


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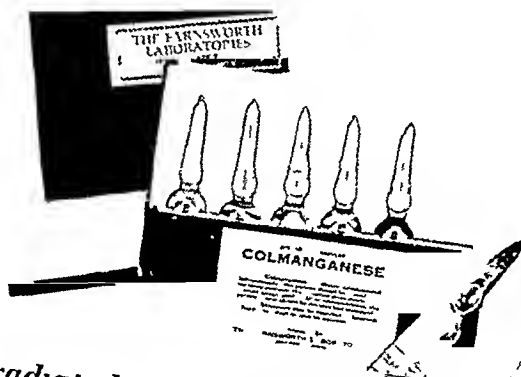
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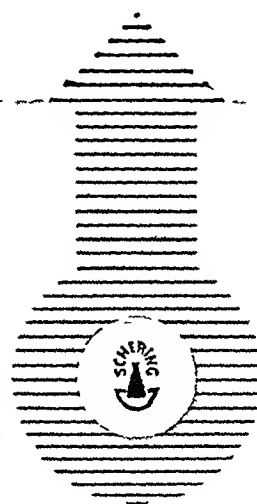
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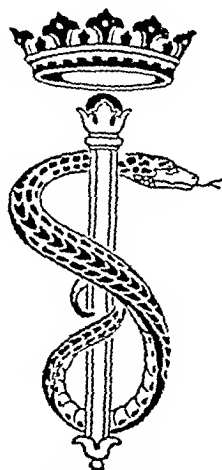
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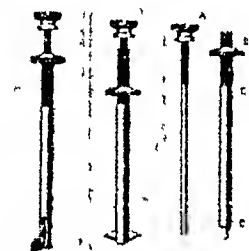


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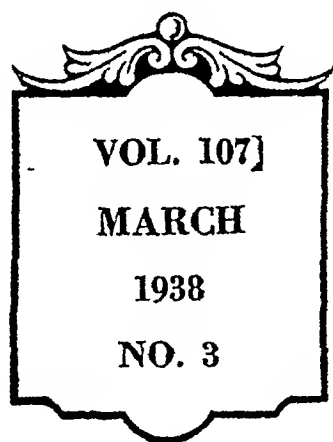


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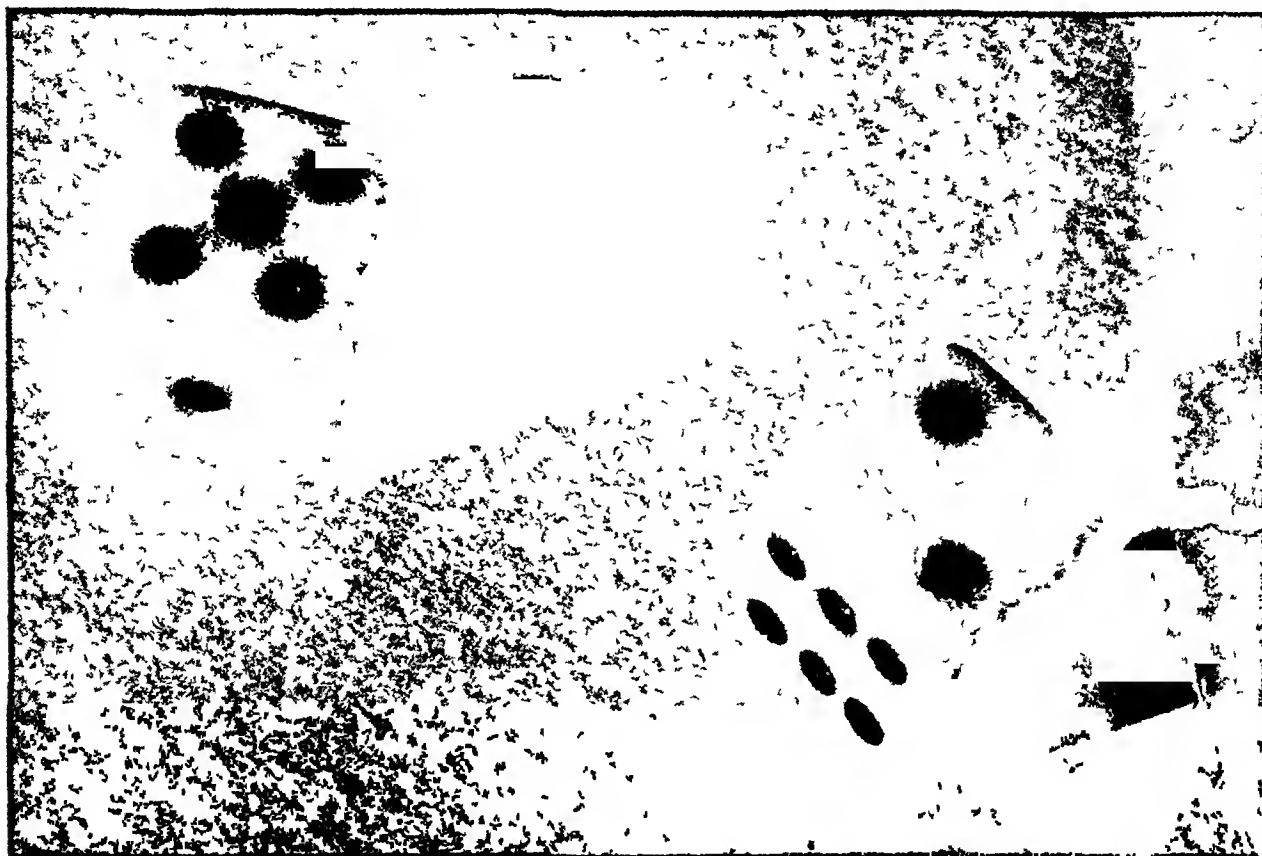
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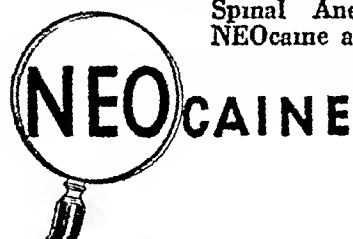
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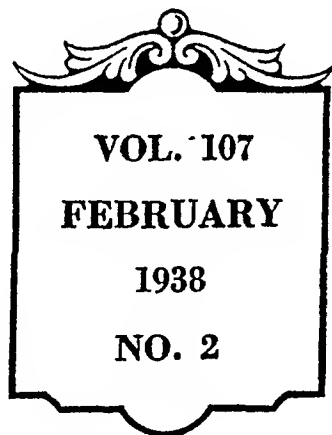
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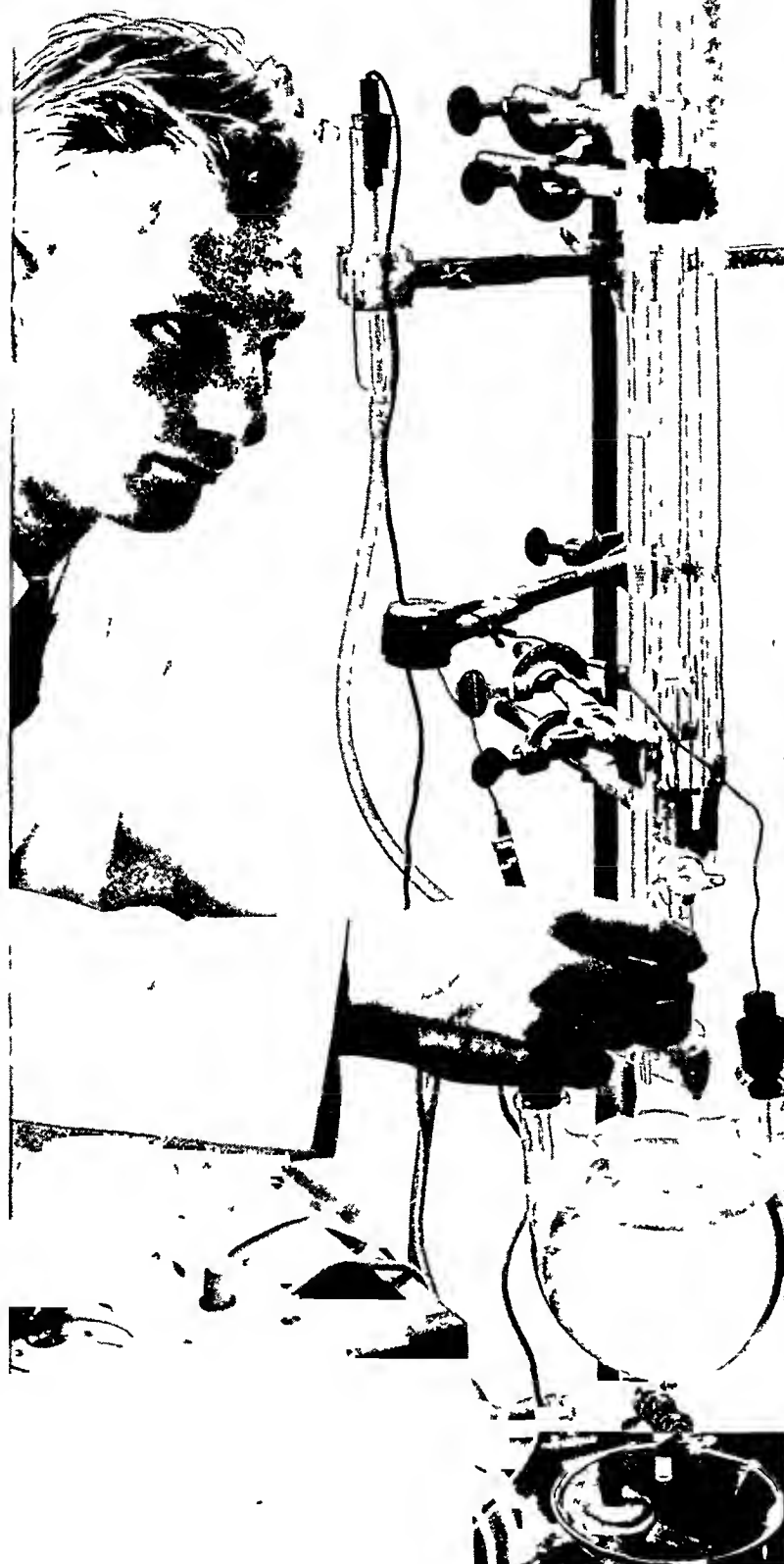
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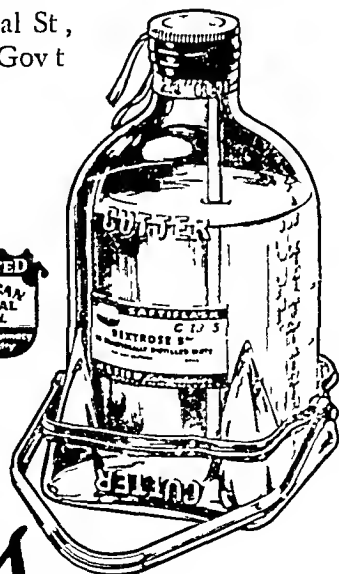
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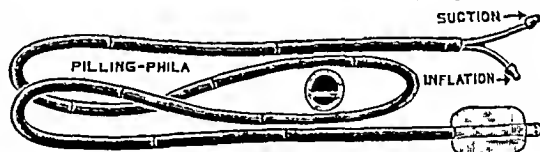
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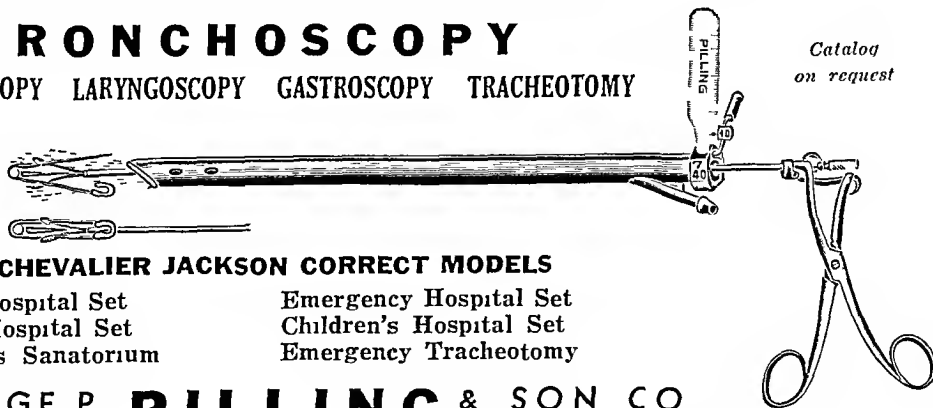
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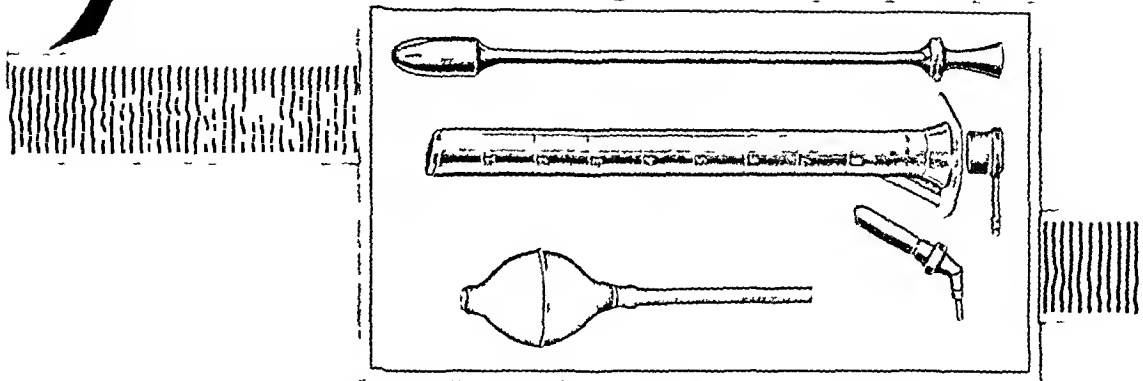
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ARCH & 23rd PHILADELPHIA

# Yeomans'



## Proctoscope.

The Yeomans Proctoscope consists of a tube 10 inches long with a working length of 8 inches graduated in eight one inch divisions. Its distal end is slightly oblique and the proximal end is fitted with a large flange having a milled edge. A small segment is cut from one side to prevent rolling. An auxiliary tube to accommodate a light carrier perforates the flange and joins the main tube at an angle.

Illumination is direct and is obtained from a small powerful electric bulb covered with a capsule holding a plano convex lens so set that the collected rays are refracted at a compensating angle to the light carrier. The light carrier fits accurately into the auxiliary tube by means of a conical fitting so that only the lens projects into the main tube. Therefore all the rays are focused at the distal end. The vision of the observer and the path for the introduction of the instruments for examination local application or operation are always clear there being no obstruction.

A lens cap closes the proximal end of the proctoscope tube and contains a glass window which magnifies the illuminated field at the distal end of the tube. Fastened to the side of this lens cap is a nipple which provides for the attachment of a hand bulb to inflate the bowel. The conical fittings of the lens cap and light carrier prevents the escape of air when pneumatic pressure is applied. The obturator has an olivary tip which facilitates the introduction of the tube. The tubes are made in various sizes.

### YEOMANS' PROCTOSCOPE

Yeomans Proctoscope (Catalogue No 293) complete with 10 x  $\frac{7}{8}$  tube and obturator, light carrier, conducting cord, lens cap, lamp and inflation bulb without case \$35.00

- Proctoscope Tube 10 inches long (8 inch working length)  $\frac{3}{4}$  inch in diameter
- Proctoscope Tube 12 inches long (10 inch working length)  $\frac{3}{4}$  inch in diameter
- Infant Proctoscope Tube 10 inches long (8 inch working length)  $\frac{1}{2}$  inch in diameter
- Sigmoidoscope Tube 14 inches long (12 inch working length)  $\frac{3}{4}$  inch in diameter

The same light carrier fits all the above tubes. In practice it will be found that the most useful size which will fill the requirements in the majority of cases is the 10 inch by  $\frac{7}{8}$  inch tube (8 inch working length).

The entire instrument may be carried in the physician's bag and for this reason it is supplied without a case. All parts of the instrument which come in contact with the patient may be sterilized by boiling.

ESTABLISHED IN 1900



BY REINHOLD H. WAPLER

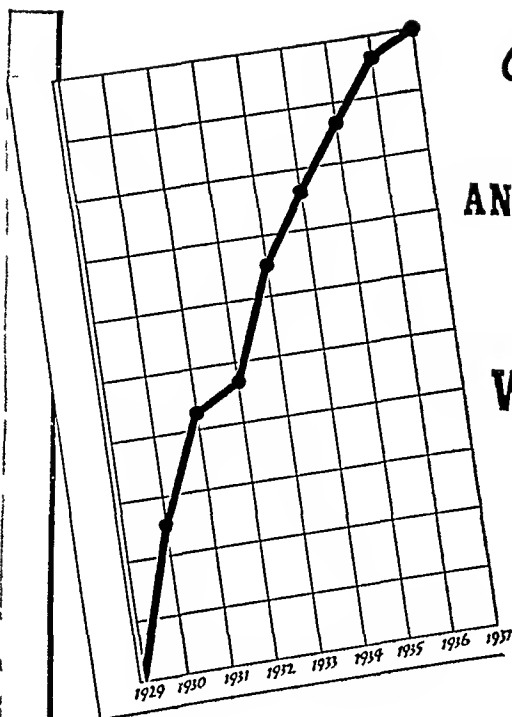
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continued confidence of anesthetists and surgeons in this basal anesthetic agent, as attested by the progressive increase in its use since the commercial introduction in 1930. In the last eight years more than 1000 publications have appeared dealing with practically every feature of its application in general surgery and the specialties. This includes reports from many of the outstanding medical institutions in America.

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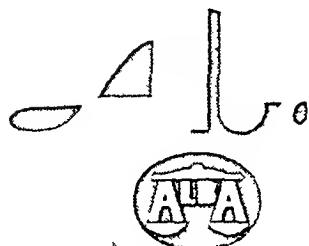
**Skin Left Soft and Supple.** No chapping of skin during cold weather No brittle nails

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67 683 688 Nov  
1938

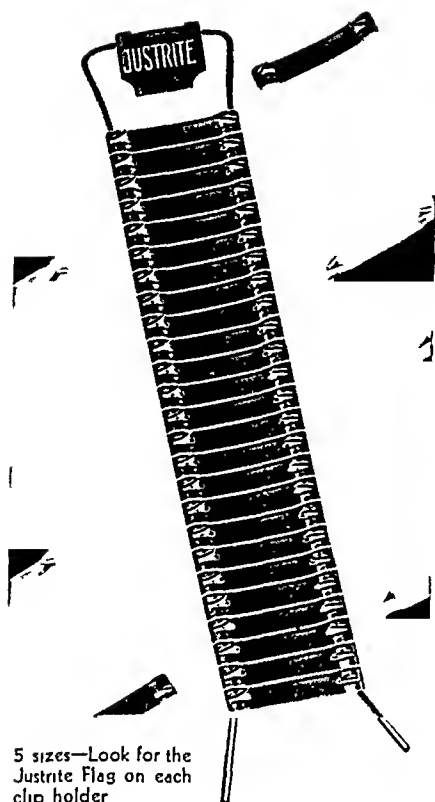
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FIVE-O CATGUT (ooooo) differs from any material previously produced in fineness of size—coupled with exceptional strength, gradual absorption rate, and freedom from reaction

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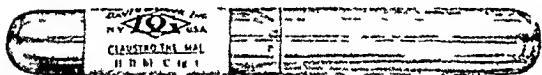
THE non-boilable variety of D & G Kalmerid Catgut. It possesses the maximum practical flexibility without loss of other equally essential qualities. It is subjected to rigorous heat sterilization in the manufacturing process. It is free from oils and will not slip at the knot. Its moisture content is *normal* so it is free from the progressive deterioration in strength typical of water-logged catgut.

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1405 Plain Catgut	approx 5'
1425 10-Day Chromic	" 5'
1445 20-Day Chromic	" 5'
1485 40-Day Chromic	" 5'

Sizes 4-0 000 00 0 1 2 3 4

Package of 12 tubes of a kind \$3 60

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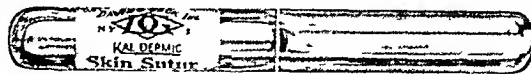
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NO	LENGTH
1205 Plain Catgut	approx 5'
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Sizes 000 00 0 1 2 3 4

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## Kal-dermic Skin Sutures



A NON-CAPILLARY, heat sterilized suture of unusual flexibility and strength. It is uniform in size, non-irritating, and of distinctive blue color. Boilable.

NO	SUTURE LENGTH	DOZEN
550 Without Needle	120"	\$3 60
953 With Full-Curved Needle	20"	3 00
954 With Half-Curved Needle	20"	3 00

Sizes 000 (FINE) 00 (MEDIUM) 0 (COARSE)

852 Without Needle 40" 1 80

Sizes 8-0 6-0 4-0 000 00 0

In packages of 12 tubes of a kind and size

## Kal-dermic Tension Sutures

IDENTICAL in all respects to Kal-dermic skin sutures but larger in size.

NO	SUTURE LENGTH	DOZEN
555 Without Needle	60"	\$3 60
855 Without Needle	20"	1 80

Sizes 1 2 3 4  
(FINE) (MEDIUM) (COARSE) (EXTRA COARSE)

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30 Chromic Without Needle	3 60
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38 1/2-Circle, 2" Cutting Point Needle	4 20

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# Heat Sterilized

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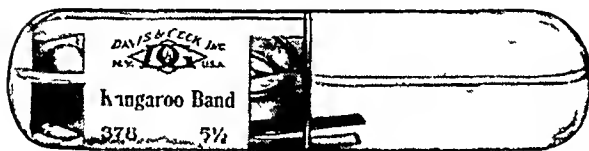
**G**ENUINE tendons selected for uniformity and strength Chromicized to resist absorption in fascia or in tendon for approximately thirty days Tendon lengths vary from 12 to 20 inches Two varieties Boilable and Thermo-flex (non-boilable)

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380	Claustro-Thermal ( <i>boilable</i> )

Sizes 0 2 4 6 8 16 24

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## Kangaroo Bands



**K**ALMERID kangaroo tendons with a flattened area in the center, for the surgical treatment of fractures Prepared with flattened areas in the following lengths 4½, 5½, and 6½ inches

NO	
378	Thermo-flex ( <i>non-boilable</i> )

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## Unabsorbable Sutures



NO		LENGTH	SIZES
350	Celluloid - Linen	60"	000, 00, 0
360	Horsehair	168"	00
390	White Silkworm Gut	84"	00, 0, 1
400	Black Silkworm Gut	84"	00, 0, 1
450	White Twisted Silk	60"	000 to 3
460	Black Twisted Silk	60"	000, 0, 2
480	White Braided Silk	60"	00, 0, 2, 4
490	Black Braided Silk	60"	00, 1, 4

BOILABLE

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**T**HREADED on half-curved or full-curved eyed needles with cutting edges for skin, muscle, or tendon Boilable



WITH HALF-CURVED NEEDLES

NO		LENGTH	SIZES
904	Plain Catgut	20"	00 to 3
924	20-Day Chromic Catgut	20"	00 to 3
954	Kal-dermic	20"	000, 00, 0
964	Horsehair	two 28" strands	00
974	White Silkworm Gut	two 14" strands	0
984	White Twisted Silk	20"	000, 0, 2
900	Assorted Catgut, Silk, and Kal-dermic		



WITH FULL-CURVED NEEDLES

903	Plain Catgut	20"	00 to 2
923	20-Day Chromic Catgut	20"	00 to 2
953	Kal-dermic	20"	000, 00, 0
963	Horsehair	two 28" strands	00
973	White Silkworm Gut	two 14" strands	0
983	White Twisted Silk	20"	000, 0, 2
930	Assorted Catgut, Silk, and Kal-dermic		

Package of 12 tubes of a kind \$3 00

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**I**N addition to the foregoing a wide variety of suture-and-needle combinations is available for intestinal, thyroid, tonsil, eye, harelip, cleft palate, plastic, nerve, artery, obstetrical, circumcision, ureteral, renal, and dental surgery

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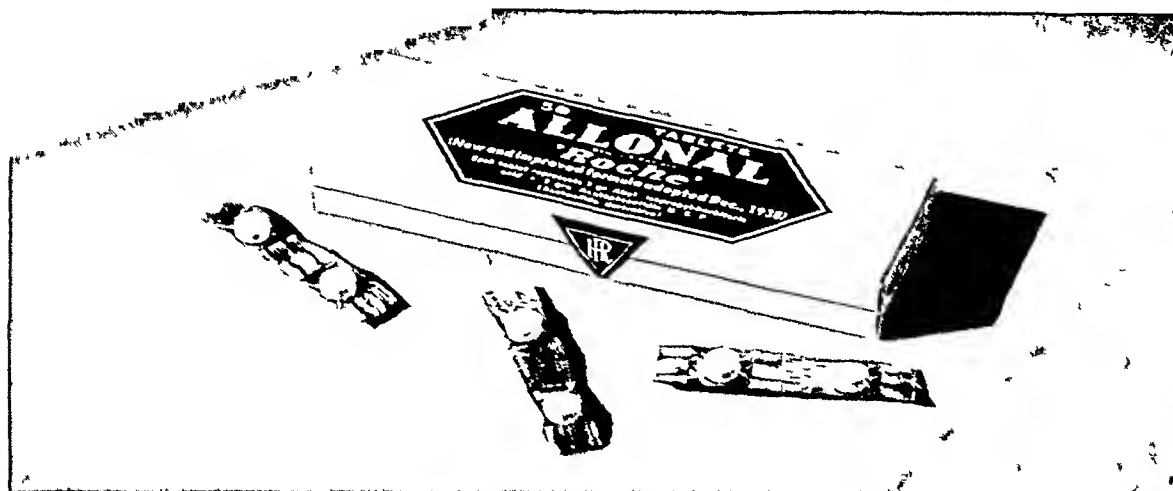
GILBERTUS ANGLICUS is credited with the first extirpation of gonorrhea with the knife. His *Compendium*, written in 1240, reveals him as an ardent advocate of cleanliness in wound treatment. In scalp wounds he used interrupted silk sutures and kept the most dependable angle open for drainage with a soaking wick. In the treatment of nerve injuries, however, he recommends a dressing of earthworms lightly beaten in mortar and mixed with hot oil.

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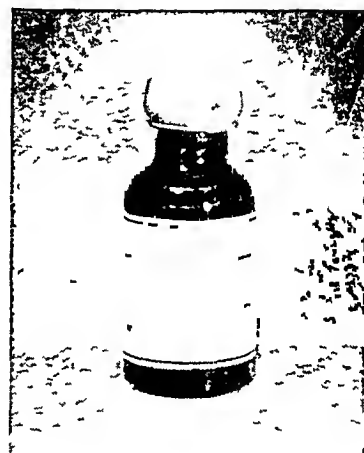
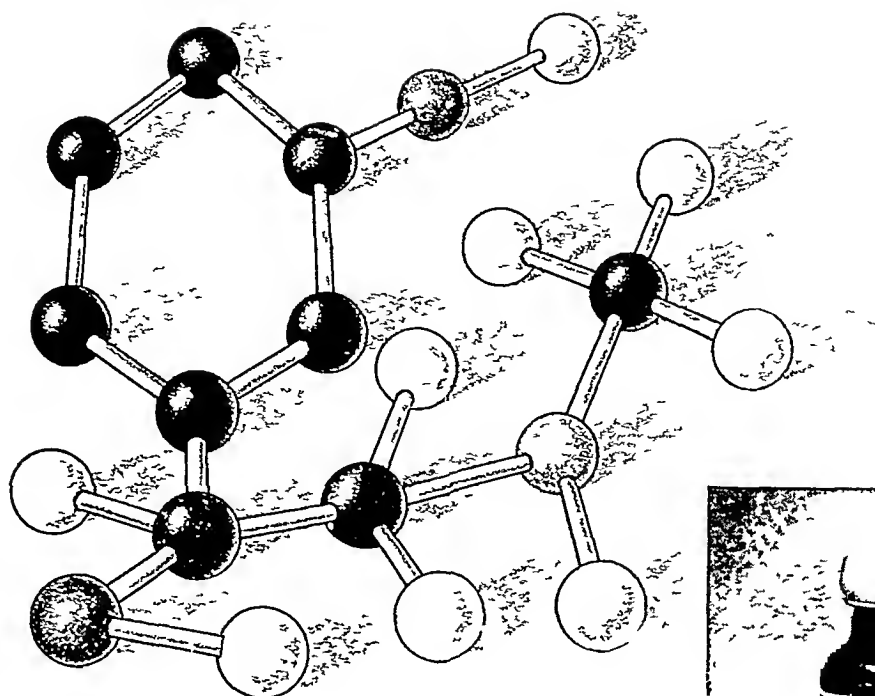
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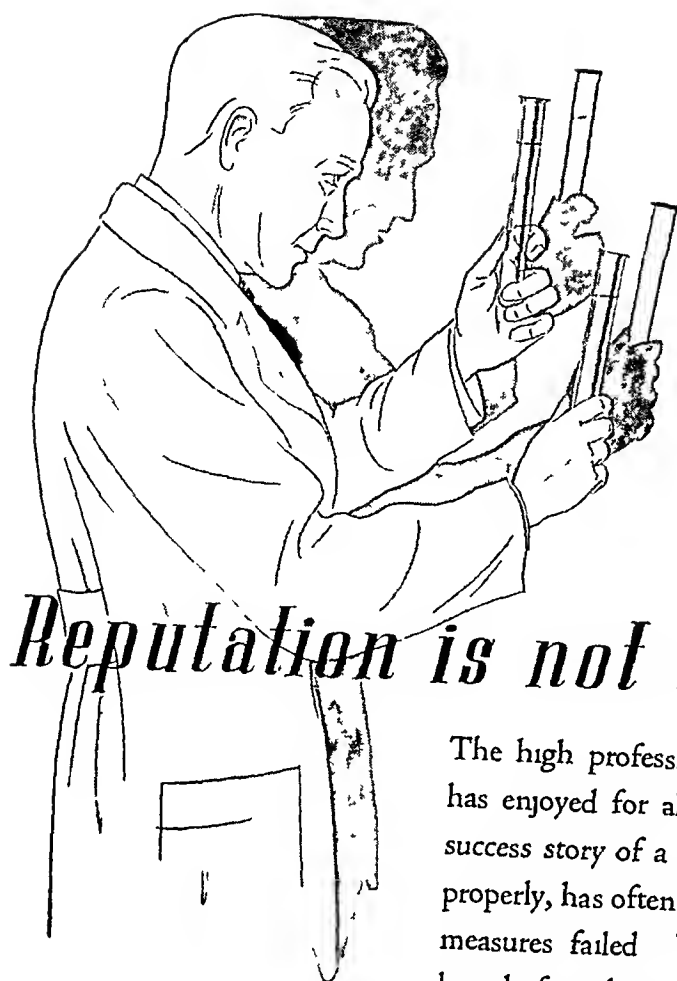
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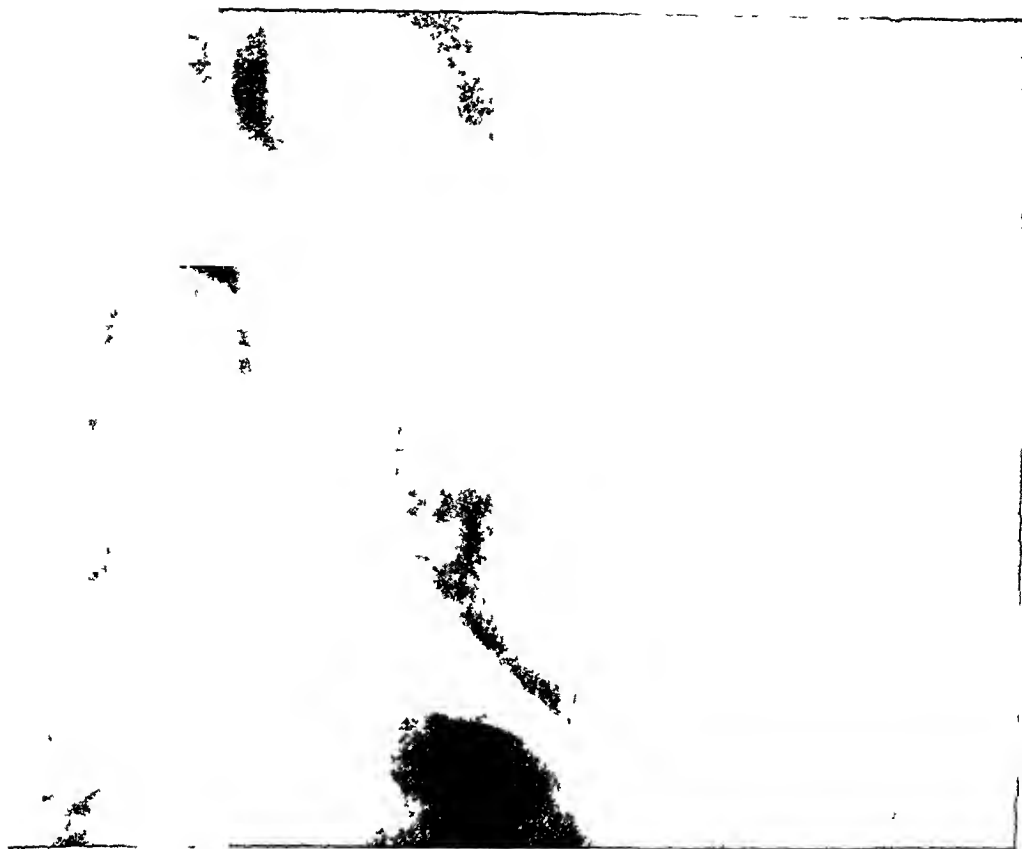
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<i>Constituents</i>	Tincture Gentian	Tincture Taraxacum
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*How Supplied* Bottles of 6 oz and 16 oz

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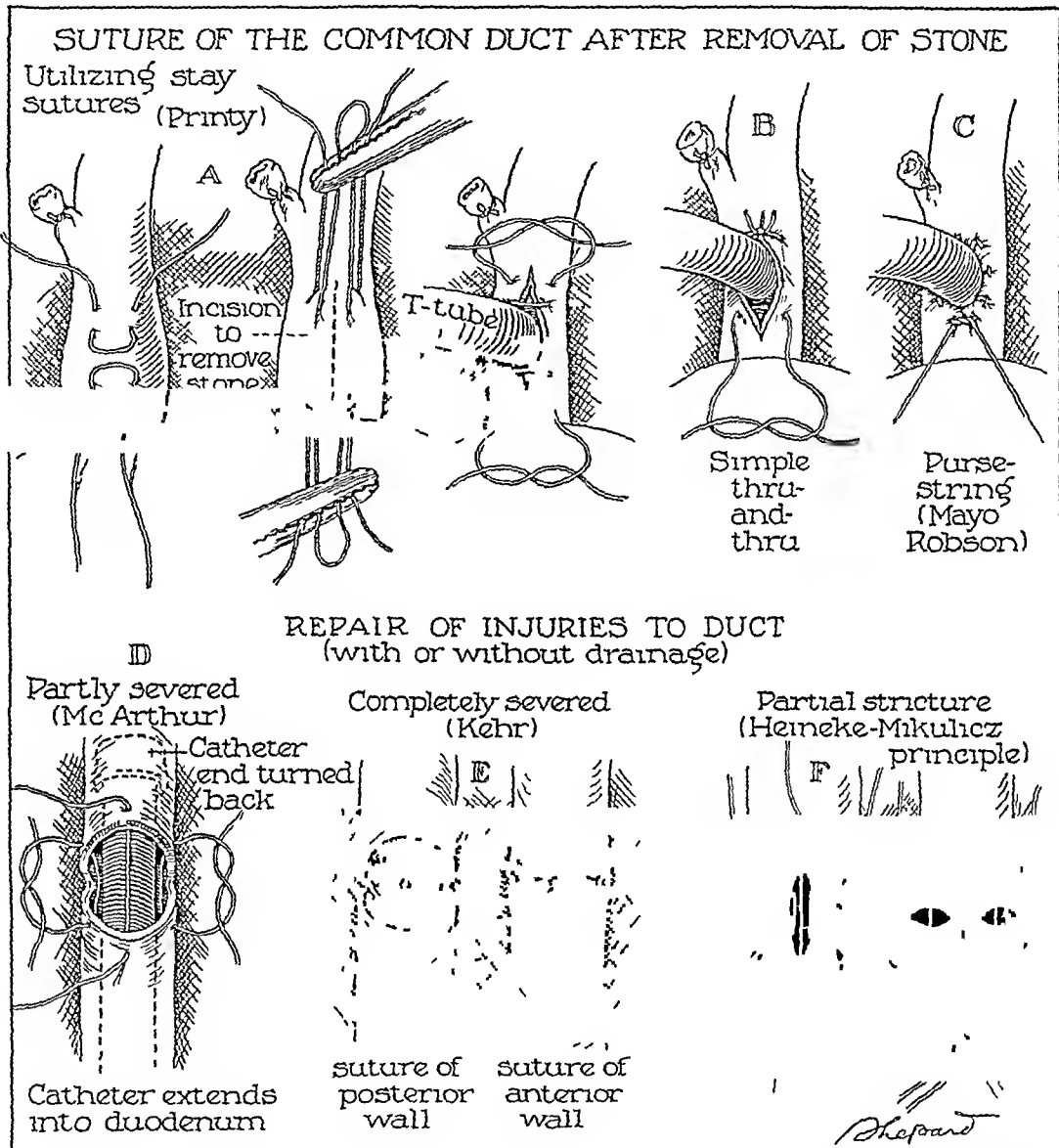
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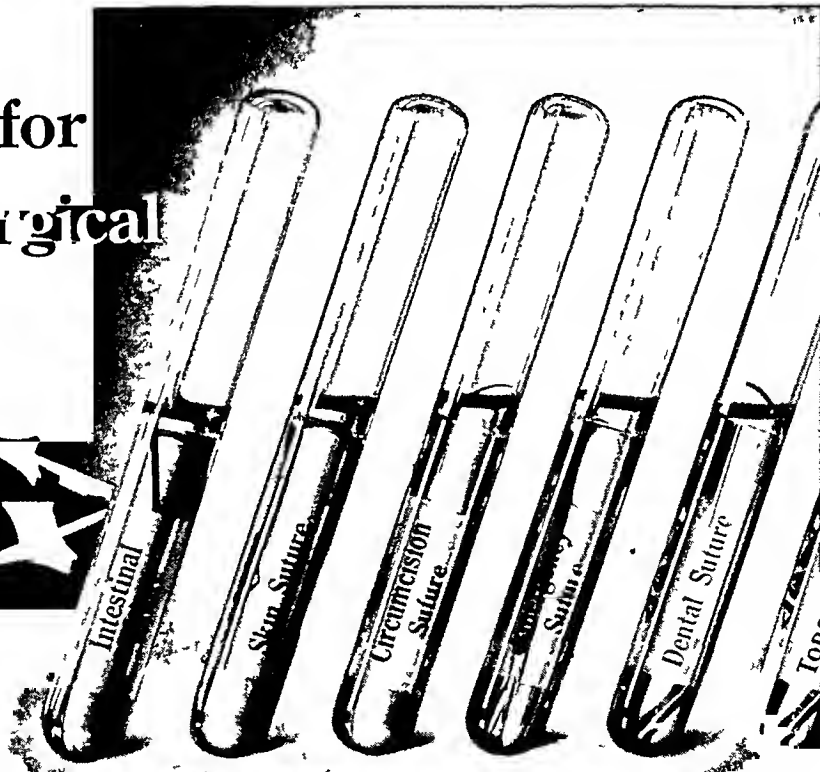
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## SEGMENTAL PNEUMONECTOMY IN BRONCHIECTASIS

THE LINGULA SEGMENT OF THE LEFT UPPER LOBE

EDWARD D CHURCHILL, M D

BOSTON, MASS

AND

RONALD BELSEY, F R C S

LONDON, ENGLAND

FROM THE THORACIC CLINIC AND SURGICAL SERVICES OF THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS

A NEW chapter in surgical anatomy dedicated to the detailed structure of the lung has been opened by the operative surgery of bronchiectasis and a more precise study of the pathology of that disease. Solely as a concession to operative technics, the lobe has been considered the surgical unit of the lung. The very name of the operation of lobectomy indicates the general acceptance of this concept.

A lobe is merely a segment of lung bounded by more or less constant and complete external fissures. It has been the convenience of these fissures rather than the underlying pathology that has defined the areas for pulmonary resection. A lobe of the lung, however, is in reality made up of a cluster of bronchopulmonary segments.

Greater precision in diagnosis and operative technic now indicates that the bronchopulmonary segment may replace the lobe as the surgical unit of the lung. This concept is developed in presenting the diagnostic and surgical aspects of the lingula segment of the left upper lobe. The basic principles of the concept, however, transcend the importance of this one bronchopulmonary segment and their wider application will be referred to briefly.

Bronchiectasis is frequently limited to one or more bronchopulmonary segments within a lobe, the remainder of the lobe being normal. It also tends to be primarily multilobar in its distribution. In a series of 86 cases of bronchiectasis operated upon by one of the authors (E D C) at the Massachusetts General Hospital, the disease was limited to the confines of a single lobe in only 20 per cent. This characteristic of the disease provides a rational basis for proposing the resection of diseased bronchopulmonary segments from several lobes, if necessary, with the conservation of normal lung segments, rather than continuing with the removal of entire lobes as unit structures. This principle finds particular application in early cases of bronchiectasis and those with a bilateral distribution.

An accurate appraisal of the extent and distribution of bronchiectatic

areas requires precision in the technic and interpretation of lipiodol bronchography and insistence upon complete visualization of not only the main bronchi but of every secondary and tertiary branch bronchus as far as its finer ramifications. Such detailed study is essential in nearly every case if a practical working basis is to be established for eradication of the disease by surgical methods.

Satisfactory surgical results in bronchiectasis can be achieved by the removal of all diseased segments of lung tissue, but the removal of a single lobe in a case of multilobar disease can lead only to disappointment unless the operation is undertaken as a palliative rather than a curative measure. A failure to delineate the complete pattern of the disease before the operation is the first step toward unsatisfactory operative results.

In our experience, bronchiectasis usually has reached its full extent and distribution at the time the diagnosis is made. The concept that bronchiectasis spreads insidiously from lobe to lobe has received undeserved support from the fortuitous demonstration of dilated bronchi by incomplete bronchograms in varying portions of the lung at different examinations. In rare instances a spread of bronchiectasis has been observed, usually as a sequel to an acute pneumonic episode. In general, however, the anatomic pattern of the disease remains static over long periods of time although the symptoms are notoriously subject to variation. Any attempt to explain an unsatisfactory surgical result on the basis of postoperative extension of the disease appears contrary to the observed facts of preoperative pathology.

A recent survey of the Massachusetts General Hospital cases revealed that the lingula is also involved sufficiently to demand resection in at least 80 per cent of the cases of bronchiectasis of the left lower lobe, the most common site of the disease. The disappointing clinical results of some lobectomies can be explained by the failure to appreciate this high incidence and the perpetuation of cough and sputum attributed to residual disease in an unresected lingula. The lingula process of the left upper lobe stands, therefore, as an anatomic entity of great practical significance.

*The Surface Anatomy of the Lingula*—It has been suggested by Nelson<sup>8</sup> that each lung is normally composed of four lobes. Upper, middle, lower and dorsal.\* The evidence presented in support of this suggestion depends upon

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\* The "dorsal lobe" is the synonym for the apical portion of the lower lobe. It is supplied by the first dorsal branch of the lower lobe stem bronchus, arising opposite the middle lobe bronchus on the right, and 1 to 2 cm. below the upper lobe bronchus on the left. The artery to the dorsal lobe arises from the inferior of the two main divisions of the pulmonary artery, close to its origin, and passes downward and medially, posterior to the main stem bronchus. The vein from the dorsal lobe drains into the inferior pulmonary vein (Fig. 5). Well developed fissures between the dorsal lobe and lower lobe proper are seen occasionally, and not infrequently the plane of cleavage is indicated by an incomplete horizontal fissure at the level of, or below, the fissure between the middle lobe and the upper lobe. This fissure is seen more commonly on the right side than on the left, especially in the lungs of children. Deve<sup>3</sup> records a well defined fissure in 20 out of 180 lungs examined. Levitin and Brunn<sup>7</sup> have also described the two major broncho-vascular segments that make up the lower lobe, with particular emphasis on the embryology and roentgenologic appearance.

(1) The demonstration by dissection of four major bronchovascular segments in each lung, and (2) the not infrequent occurrence of rudimentary fissures constant in position but not in degree of development subdividing the lung into four lobes. Each lobe possesses an independent bronchus and blood supply and is separated from the adjacent lobes by either a complete or partial fissure, or by an avascular plane of cleavage across which no vascular communications are encountered until the hilum is approached.

For descriptive purposes the lingula process may be considered as the homologue of the right middle lobe although embryologists are not unanimous in accepting this designation. It occupies a corresponding position but, whereas the fissure between the right upper and middle lobes is usually well developed, this is uncommon on the left side.

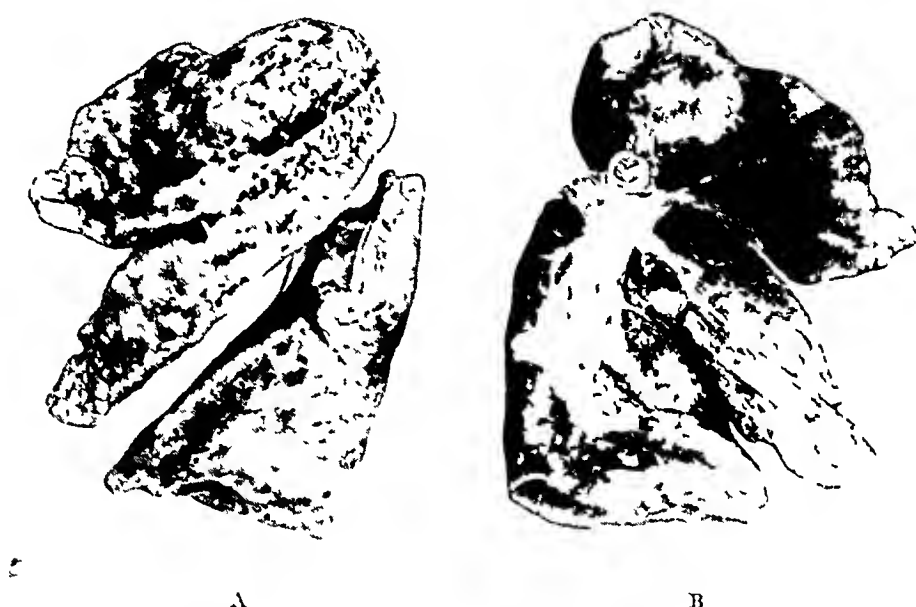


FIG. 1.—Normal human left lung showing well developed fissure between the upper lobe and the lingula.

Figure 1 demonstrates a left lung in which the fissure between the upper lobe and lingula is well developed except posteriorly, a rudimentary dorsal lobe fissure is also present in this specimen. When the fissure between the left upper lobe and lingula is not well developed its position is indicated by a notch on the anterior margin of the lung. The fissure is commonly more pronounced on the mediastinal than on the costal surface of the lung (Fig. 2).

The lingula, when well developed, resembles the right middle lobe in shape and exhibits a quadrilateral mediastinal surface, a semielliptical inferior or interlobar surface and a triangular anterolateral or costal surface. A prominent ridge or "frenum" separates the mediastinal and inferior surfaces and extends upward and backward to the hilum. In the posterior end of this ridge are situated the bronchus and blood vessels supplying the lingula.

Hovelacque *et al*<sup>6</sup> have reported two cases of trilobar left lungs and Chauri<sup>2</sup> another in which the extrapulmonary course of the lingula bronchus

resembled that of the right middle lobe bronchus, having an independent origin from the left lower lobe stem bronchus

*The Lingula Bronchus*—The anatomy of the lingula bronchus was described by Ewart,<sup>5</sup> in 1889, in his monograph on the bronchi and pulmonary blood vessels. Ewart referred to the lingula as the "cardiac lobe," and on the evidence of dissections and bronchial casts described a "cardiac stem bronchus" arising from the inferior aspect of the upper lobe bronchus about 1 cm from its origin, dividing after a 2 to 3 cm course into anterior and posterior cardiac branches, the anterior again dividing into medial or sternocardiac, and lateral or mammary cardiac branches. Further subdivisions were described in detail.

The lingula bronchus arises from the inferior aspect of the left upper lobe

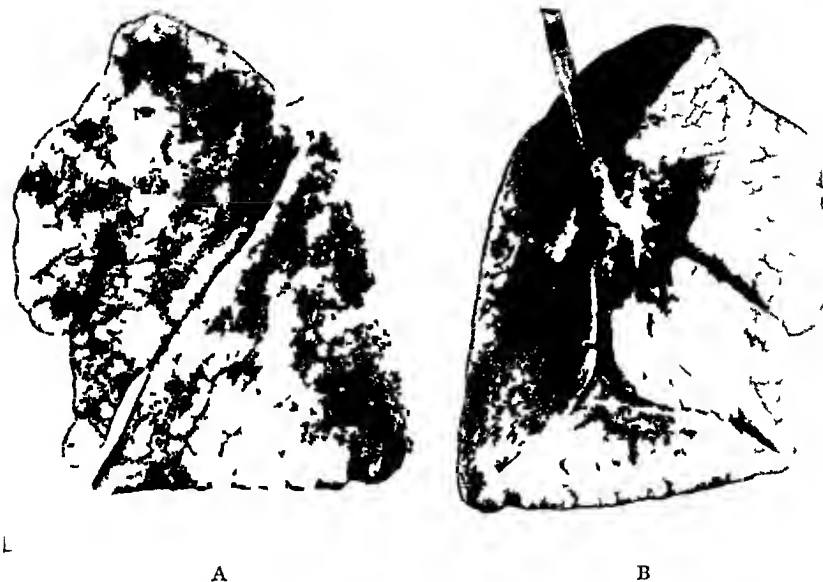


FIG 2—Normal human left lung showing the lingula fissure well developed on the mediastinal surface and the characteristic notch on the anterior border of the lung. The lingula bronchus has been dissected to demonstrate its origin from the upper lobe bronchus and its bifurcation.

bronchus 1 to 2 cm from its origin and runs downward and forward. It terminates by division into two branches, an anterolateral and a posteromedial (Fig 3).

In our own material, consisting of dissections of the human lung and lipiodol bronchograms, certain minor variations in the mode of origin of the lingula bronchus and the axillary branch of the upper lobe bronchus were encountered. Figure 4A represents the more common arrangement. Occasionally the lingula bronchus and the axillary branch of the upper lobe bronchus arise by a common stem from the main upper lobe bronchus as demonstrated in Figure 4B. Variations are also encountered in the distance of the orifice of the lingula bronchus from the orifice of the upper lobe

bronchus, and in the length of the lingula bronchus proximal to its first division

*The Blood Supply to the Lingula*—The branch of the pulmonary artery supplying the lingula arises from the main arterial trunk above the level of

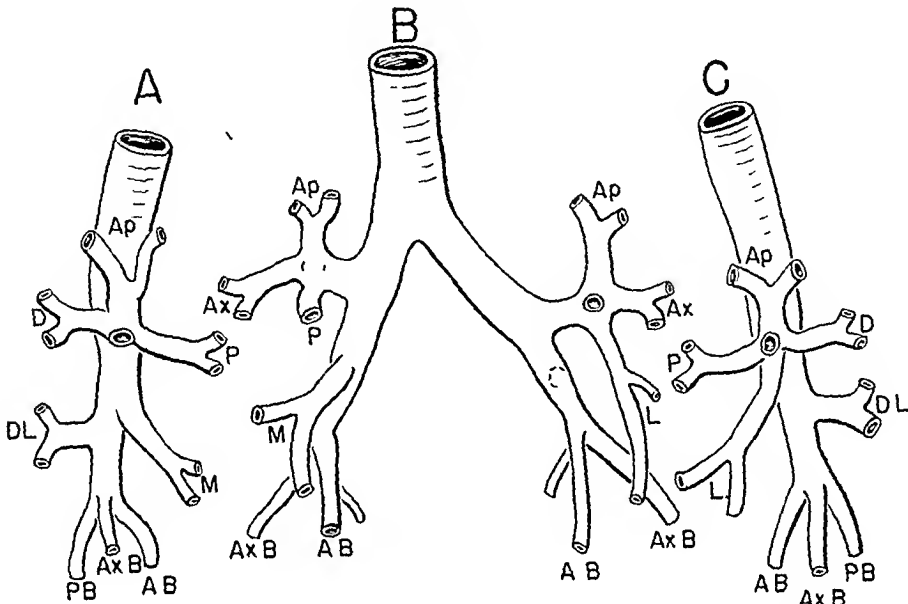


FIG 3—Diagrammatic representation of the normal bronchial tree (A) Right lateral view (B) Anteroposterior view (C) Left lateral view (Ap) Apical division of the upper lobe (Ax) Axillary division of upper lobe (P) Pectoral division of upper lobe (D) Dorsal division of upper lobe (L) Lingula bronchus (M) Right middle lobe bronchus (DL) Dorsal lobe bronchus (AB) Anterior basic division of the lower lobe (Ax B) Axillary basic division of the lower lobe (PB) Posterior basic division of lower lobe

the origin of the upper lobe bronchus, behind which it runs downward and laterally, continuing its course lateral and slightly posterior to the lingula bronchus (Fig 5) The main artery divides into two branches which follow closely the two primary divisions of the lingula bronchus, the artery accom-

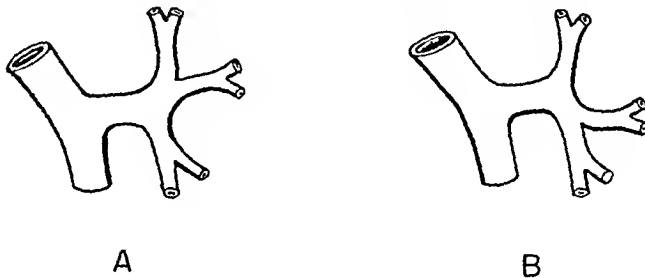


FIG 4—Diagrammatic representation of variations in the mode of origin of the lingula bronchus and the axillary division of the upper lobe bronchus The arrangement shown in A is the more common

panying the posteromedial division descending anterior to the anterolateral branch bronchus The lingula veins run in a plane anterior to the bronchi and arteries, and drain into a main vessel running medial and slightly anterior to the lingula bronchus to join the inferior pulmonary vein At the hilum of the lingula the vein, the bronchus and artery are encountered, in that order, dissecting laterally from the mediastinum



*Experimental Delineations of the Lingula Segment*—Injection experiments were undertaken to determine the projection areas on the surface of the lung of the bronchopulmonary segment supplied by the branches of the lingula bronchus. In the first series of normal human lungs, the main lingula bronchus, and in the second series, one of the two primary divisions were injected under pressure with a viscid solution of old roentgen films in acetone, colored with aniline-black dye. The advantage of this solution as an injection material lay in its tendency to harden into a solid mass, allowing the injected bronchopulmonary segment to be dissected from the remaining lung tissue, and its shape and relations to be determined. Figure 6 demonstrates the typical appearance of a normal lung following injection of the main lingula bronchus and inflation of the remainder of the lung, and shows the area of lung

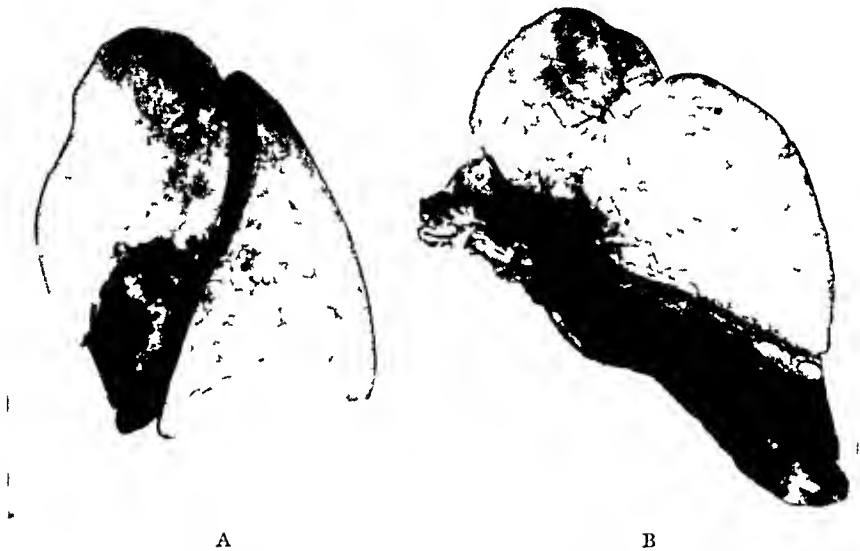


FIG 6—(A) Injection of the main lingula bronchus of a normal left lung to demonstrate the whole lingula segment. (B) Left upper lobe, mediastinal aspect.

surface in relation to that of the lingula segment. Injection of the posteromedial branch of the lingula bronchus filled the mediastinal segment of the lobe, when the anterolateral branch was injected the mass was confined to the costal segment. In a series of 20 injection experiments the bronchopulmonary segments supplied by the lingula bronchus were found to be constant in size, position and configuration.

*Clinical Visualization of the Lingula Bronchus by Lipiodol Bronchography*—A modification of the bronchography technic, evolved by Erwin,<sup>4</sup> was employed in obtaining the bronchograms reproduced in this article. The patient receives sodium pentobarbital G1 1½ one-half hour before the injection. The preliminary use of this drug appears to diminish the incidence of cocaine reaction. The pharynx and one nostril are sprayed with 4 per cent cocaine solution containing adrenalin, cotton pledgets soaked in the same solution are held in each pyriform fossa on Negus laryngeal forceps for two minutes to anesthetize the superior laryngeal nerves. A fine, rubber urethral

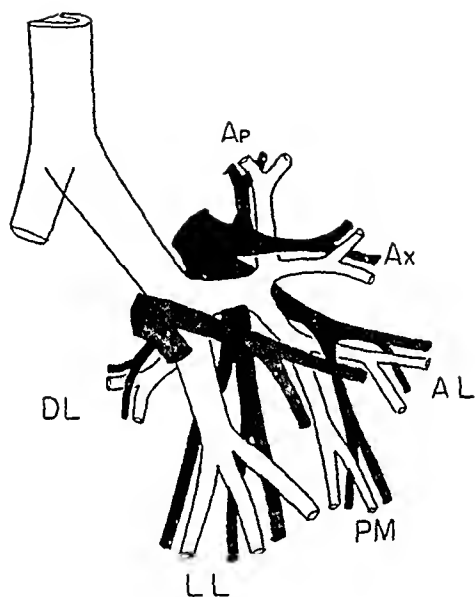


FIG 5.—Diagrammatic representation of the blood supply to the lingula. Branches of the pulmonary artery shown in red and the veins in blue. (Ap) Apical division of upper lobe. (Ax) Axiillary division of upper lobe. (AL) Anterolateral division of the lingula. (PM) Posteromedial division of the lingula. (DL) Dorsal lobe branches. (LL) Lower lobe branches.



catheter is passed through the cocaineized nostril while the patient forcibly draws his tongue forward, the tip of the catheter shows a natural tendency to enter the larynx and passes easily between the cords. Having entered the trachea, 2 cc of cocaine solution are injected through the catheter to anesthetize the tracheal and bronchial mucosa and suppress the cough reflex. The tip of the catheter lies in the lower third of the trachea and no attempt is made to pass it into the bronchi.

Certain general principles are observed during the injection. The lipiodol is used cold, when warmed the viscosity is diminished and the oil tends to run out into the alveoli. The oil is injected slowly and the cough reflex held completely in abeyance. Twenty cubic centimeters of oil are sufficient to outline both bronchial trees in an adult, less being required in a child. More information concerning bronchial pathology can be obtained by outlining the bronchial lumen with a thin, evenly distributed film of oil than by complete filling of the lumen. The side, or the suspected side, of the disease is filled first. Ideally, each lung should be filled and examined independently at three-week intervals in order that a true lateral as well as an anteroposterior film of each bronchogram may be obtained. It is not always practicable to do this and, when both lungs are to be examined at the same time, it is usual first to fill the suspected side and make the anteroposterior and lateral exposures, the other lung is then filled and further anteroposterior and oblique exposures are made. Lateral films taken with both lungs filled are dangerously misleading, owing to the superimposition and confusion of the two bronchial patterns.

With the catheter in position, the patient is placed horizontally upon the table with his shoulders supported on two pillows and the body half turned toward the left side, 6 cc of oil are slowly injected into the dorsal lobe and dorsal branches of the lower lobe bronchus. The patient is then instructed to sit up, to bend forward, and lean toward the left side, 3 cc of oil are then injected into the middle lobe or lingula bronchus and into the anterior branches of the lower lobe bronchus. The pillows are then removed and the patient lies down and is completely turned onto his left side, 3 cc of oil are then injected into the upper lobe bronchus and lateral branches of the lower lobe bronchus. A left lateral exposure is then made with the patient lying on his left side, an anteroposterior picture with the patient lying flat on his back, and, if the left lung alone is being examined, a right oblique exposure is made in the standing position. If both lungs are being examined, the patient is turned toward the right side after lateral and anteroposterior exposures of the left side have been made, and the remaining lipiodol distributed between the three positions corresponding to those used for the left lung. Less lipiodol is required to fill the second side as some tends to run over from the bronchi previously filled. Anteroposterior and right oblique exposures are then made with the patient in the erect position. The position which best demonstrates the anatomic relations of the lingula bronchus is the right oblique with the patient in the erect position (Fig 7). The advantage

of using a rubber intratracheal catheter, through which to inject the oil, lies in the ease with which the posture of the patient can be changed during the injection

*Interpretation of the Bronchogram*—No opinion can be based upon a single anteroposterior view, lateral and oblique views are essential for the interpretation of the bronchogram. The anatomy of the normal or diseased lingula can be determined only if its bronchus is completely outlined throughout its

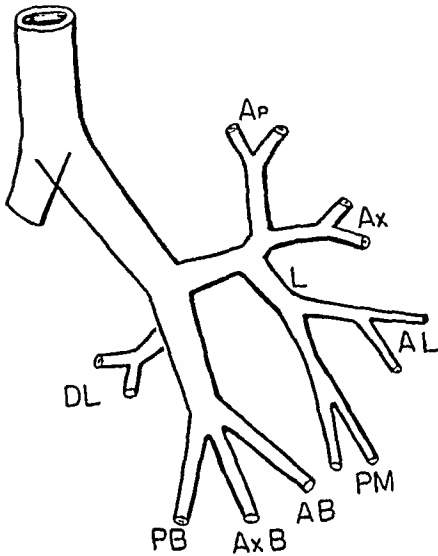


FIG 7.—Diagrammatic representation of the normal left bronchogram as visualized in the right oblique view. The distance between the orifice of the lingula bronchus and the orifice of the upper lobe bronchus has been slightly exaggerated. (Ap) Apical division of upper lobe (Ax) Axillary division of upper lobe (L) Lingula (AL) Anterolateral division of the lingula (PM) Posteromedial division of the lingula (DL) Dorsal lobe (AB) Anterior basic division of lower lobe (Ax B) Axillary basic division of lower lobe (PB) Posterior basic division of lower lobe

entire course, and its origin from the upper lobe bronchus clearly traceable, conditions which presuppose adequate filling of the upper lobe bronchus. Its first descending branch will be recognized as the lingula bronchus. Figures 8 to 11 demonstrate variations in the appearance of the bronchograms of the normal lingula bronchus in the three positions anteroposterior, left lateral and right oblique. The lingula bronchus is apt to be confused with the lower lobe bronchi in the anteroposterior position, but their differentiation presents no difficulties in the left lateral and right oblique positions. Reference to the diagrams in Figures 3, 4 and 7 will assist in the interpretation of these bronchograms, and the identification of the various branch bronchi. The position of the lingula as visualized on the bronchogram varies with the condition of the lower lobe. In general it is situated more laterally when the lower lobe is normally aerated than

when it is collapsed. After left lower lobe lobectomy the lingula swings downwards and posteriorly.

*Bronchiectasis of the Lingula Process*—In the present series of 86 cases of bronchiectasis operated upon at the Massachusetts General Hospital (by E D C), there were 55 cases in which the left lower lobe was removed as the major focus of the disease. In 44, or 80 per cent, of these 55 cases the lingula was also resected because of demonstrable bronchiectasis. In 108 cases of bronchiectasis of the left lower lobe operated upon at the Brompton Chest Hospital, London, the lingula was involved in 81, or 75 per cent.<sup>1</sup> These statistics demonstrate the great frequency with which resection of the lingula in addition to the removal of the left lower lobe is necessary to eradicate bronchiectasis of the left lung. Figures 12 and 13 demonstrate the bronchograms of two typical cases of bronchiectasis of the lingula and left lower lobe.

It has been observed that commonly the posteromedial branch of the lingula bronchus alone is diseased and only rarely are both branches involved

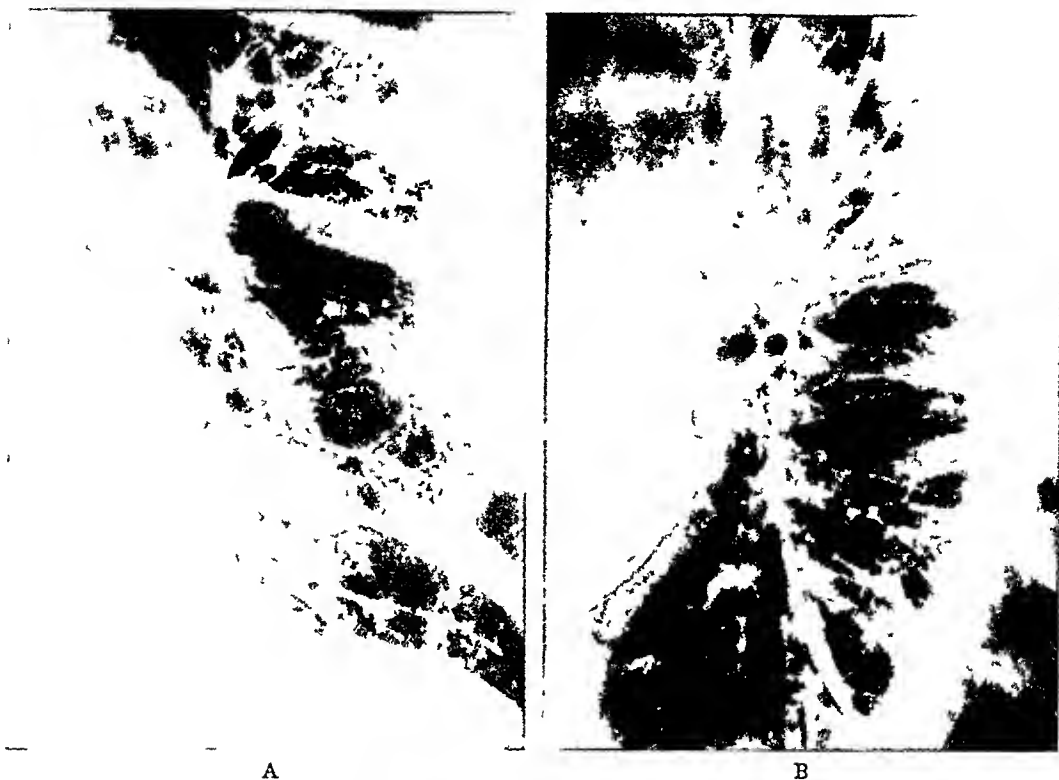


FIG 8—Normal left bronchogram (A) Anterolateral view (B) Left lateral view In the lateral view, the lumen of the axillary branch of the upper lobe bronchus is seen end on as a dark circle

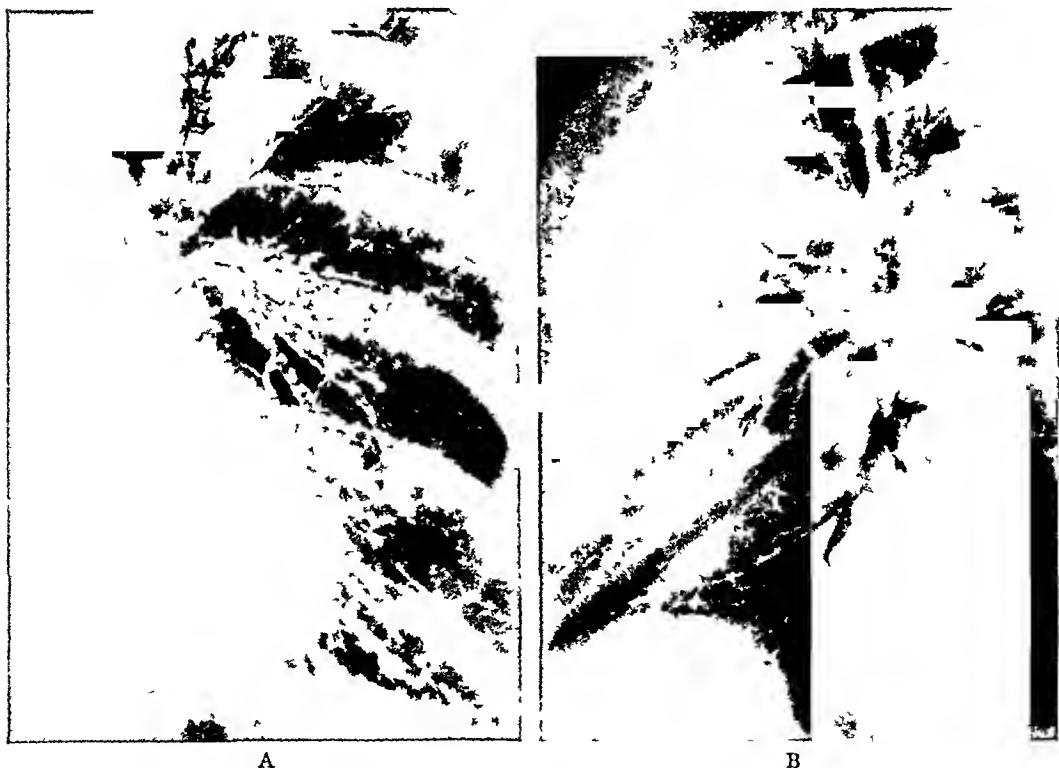


FIG 9—Normal left bronchogram (A) Anteroposterior view The pectoral branch of the upper lobe bronchus is seen descending anterior to the anterolateral branch of the lingula bronchus with which it should not be confused (B) Left lateral view Pectoral bronchus well shown just above lingula bronchus

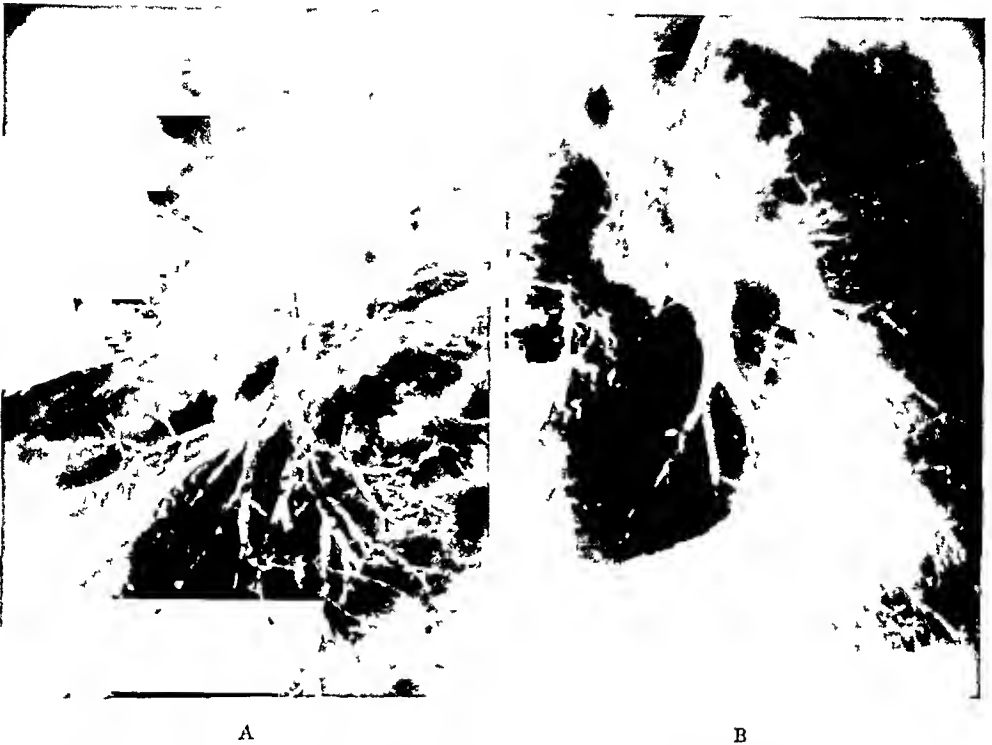


FIG 10—Normal left bronchogram (A) Left lateral view (B) Right oblique view Owing to the upward obliquity of the left upper lobe bronchus, the lingula bronchus appears to arise abnormally high in the left lateral view Origin with axillary branch as shown in Figure 4B

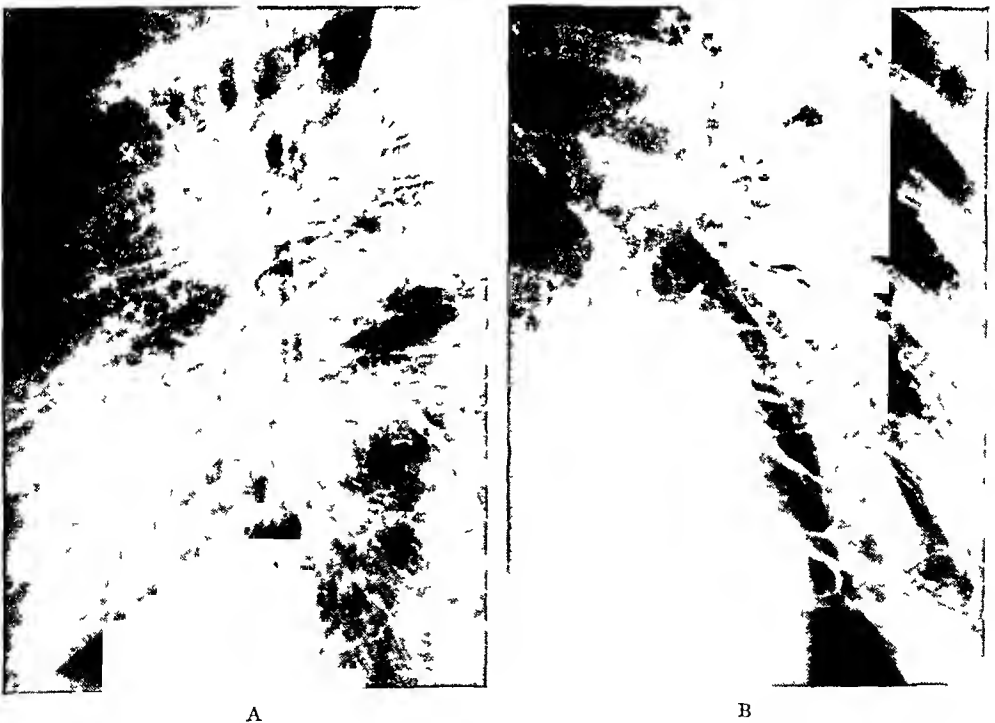


FIG 11—Normal left bronchogram demonstrating the lingula bronchus and its primary divisions (A) Left lateral view (B) Right oblique view (see Fig 7)

Bronchiectasis may be confined to, or predominant in the lingula process, but this distribution is not common, and was encountered only four times in a series of 50 cases of bronchiectasis studied by complete bronchograms. Figure 14 demonstrates a case of bronchiectasis confined to the lingula process and of sufficient severity to cause disabling symptoms. Figure 15 demonstrates a case of bronchiectasis predominant in the lingula process but with minimal involvement of a single bronchus in the left lower lobe. In Figure 16 is shown bronchiectasis of the anterolateral segment of the lingula and the right middle lobe, an unusual combination.

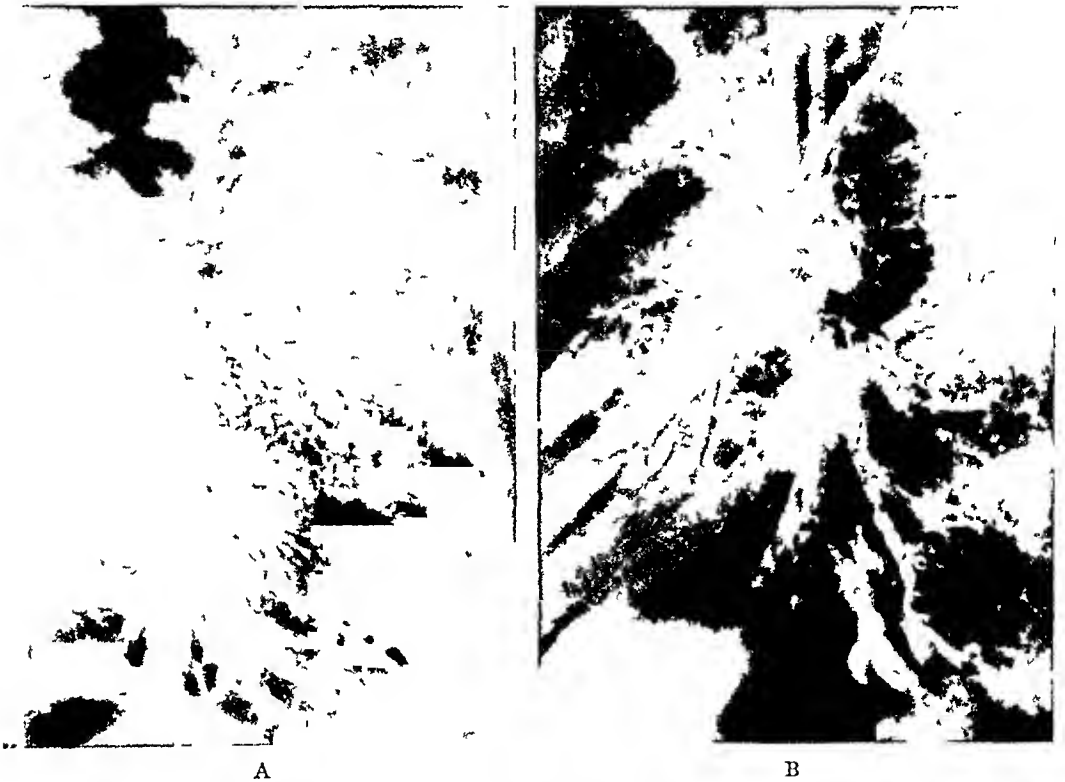


FIG. 12—Cylindric bronchiectasis of the left lower lobe and posteromedial divisions of the lingula bronchus. (A) Anteroposterior view. (B) Left lateral view.

*Residual Lingula Bronchiectasis*—Despite the fact that the lingula has been resected with the left lower lobe in 80 per cent of the Massachusetts General Hospital series, at least two patients have been observed with residual symptoms due to failure to recognize disease in this area or to resect it at the time of operation. Before the perfection of bronchographic technique, the gross appearance of the lingula at the time of operation was taken as indication for or against resection. These unsatisfactory results demonstrate that this procedure, while usually adequate, is not wholly reliable.

Patients have also been seen following lobectomy in other clinics, who complain that after removal of the left lower lobe a considerable quantity of sputum has remained. Bronchography has revealed the presence of residual bronchiectasis in the lingula process. Review of the original bronchograms, on the basis of which the lobectomy was performed, revealed either an inadequate filling of the lingula bronchus, which rendered it impossible to



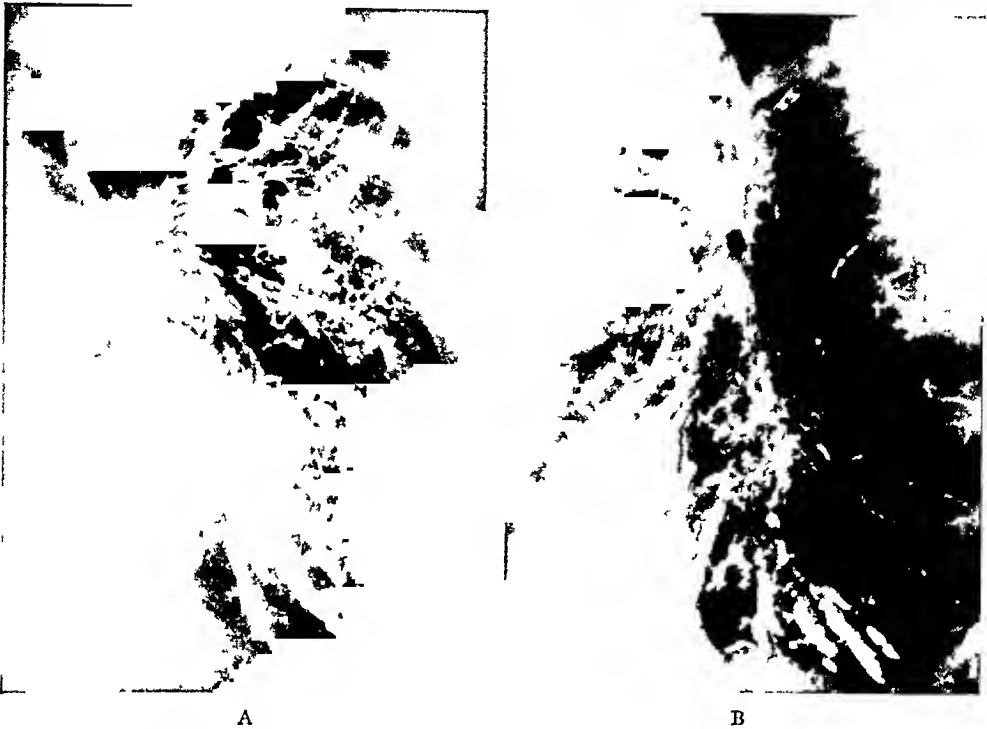


FIG 13—Cylindric bronchiectasis of the left lower lobe and posteromedial divisions of the lingula (A) Anteroposterior view (B) Left lateral view In the anteroposterior view, the disordered posteromedial branch of the lingula overlies dilated branches of the lower lobe bronchus but is clearly differentiated from them in the lateral view The anterolateral branch of the lingula is normal

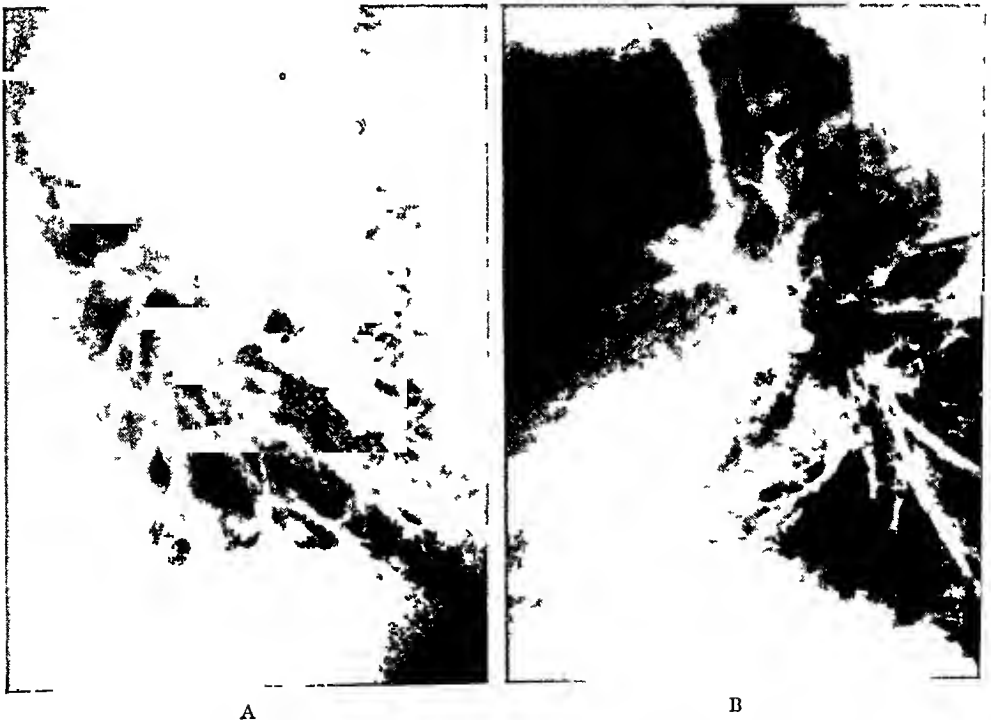


FIG 14—Cylindric bronchiectasis of both divisions of the lingula bronchus The left lower lobe is normal (A) Anterolateral view (B) Left lateral view

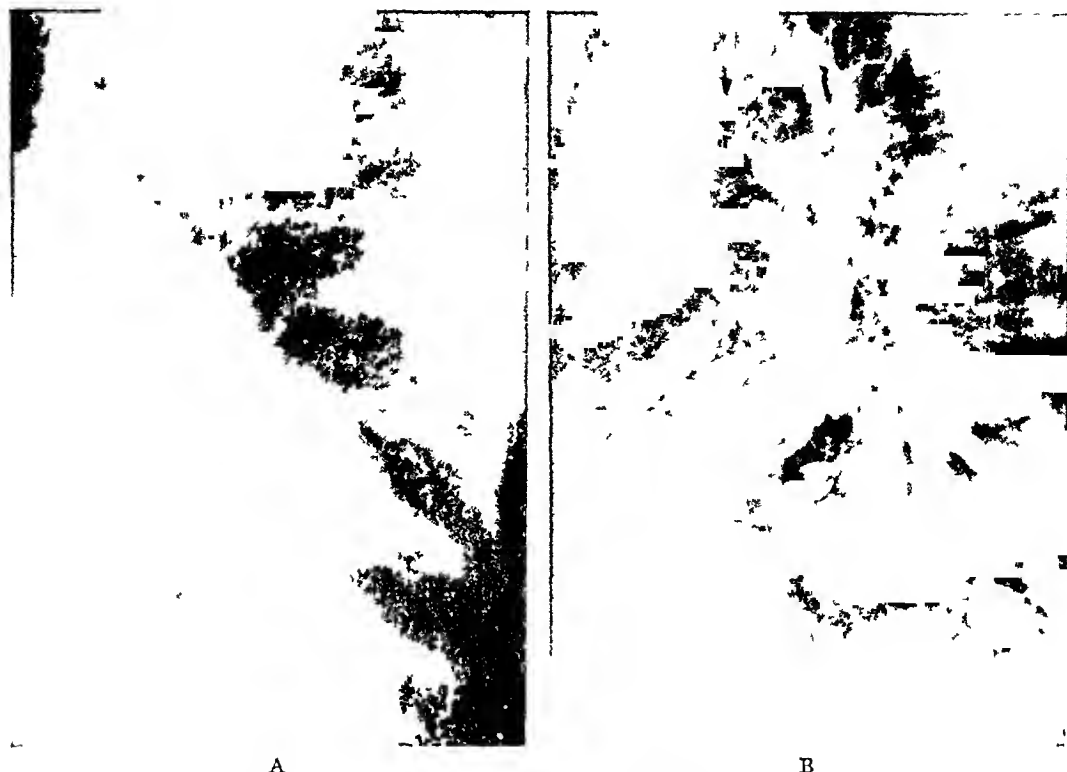


FIG 15—Cylindric bronchiectasis of both divisions of the lingula bronchus, associated with minimal disease in a single lobule of the lower lobe. (A) Anteroposterior view. (B) Left lateral view. In the lateral view, note that the pectoral branch of the upper lobe bronchus has been drawn downward toward the lingula bronchus, and that one of its terminal branches is dilated.

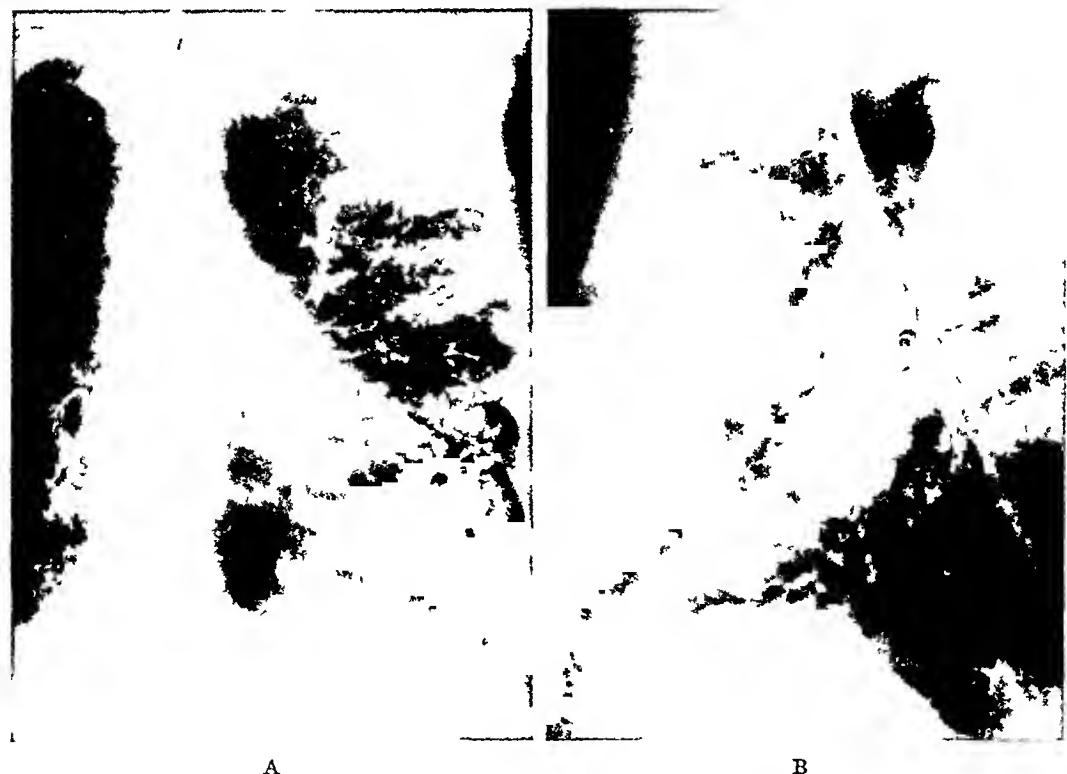


FIG 16—Saccular bronchiectasis of the lingula, disease is also present in the right middle lobe. (A) Anteroposterior view. (B) Left lateral view. In the anteroposterior view, the saccular dilations appear to communicate with the branches of the axillary basic division of the left lower lobe bronchus, but the left lateral view localizes the bronchiectasis to the lingula, and demonstrates the lower lobe to be normal.

visualize the disease present therein, or failure to interpret the film correctly. Surgery of this type will quickly cast disrepute upon the surgical treatment of bronchiectasis just as it is beginning to live down a somewhat unsavory reputation.

Persistence of symptoms due to lingula bronchiectasis is to be differentiated from the production of secretion by granulation tissue in an abnormally large lower lobe "stump," or a small persistent empyema pocket draining through the stump of the lower lobe bronchus. Both of these conditions are known to be associated with persistent cough and sputum, at least early in the

postoperative period. Figure 17 demonstrates a case of residual bronchiectasis present in the lingula and probably causing the persistence of symptoms following a lower lobe lobectomy. The qualification is made deliberately because sufficient data are not at hand to evaluate properly the rôle of the lobal stump as a cause of residual sputum. In this particular case the stump is short and presumptive evidence incriminates the lingula.

Figure 18 shows the postlobectomy bronchogram of a patient who complained that the removal of the lower lobe had only slightly diminished the volume of sputum. Bronchography revealed the presence of a residual lingula bronchiectasis. The stump of the lower lobe was also well filled by lipiodol but the operative note indicated a higher amputation than usual. Bronchoscopy disclosed a dry stump com-



FIG 17.—Postlobectomy bronchogram demonstrating the stump of the lower lobe bronchus and residual bronchiectasis in the lingula which has been displaced downward and backward. Right oblique view.

pletely epithelialized and an inflamed lingula bronchus full of pus. The lingula was resected in this case with complete relief of symptoms.

*Chronic Pulmonary Abscess of the Lingula*—In the clinical material forming the basis of this paper, there has occurred one case of abscess confined to the lingula, in a male, age 19. The abscess had been drained externally in the acute stage seven years previously, the wall of the cavity had become epithelialized and an external bronchial fistula persisted. Injection of lipiodol through the bronchocutaneous fistula outlined a cavity communicating with the anterolateral division of the lingula bronchus, and demonstrated cylindric bronchiectasis in the posteromedial division of the bronchus (Fig 19). Surgery was indicated by repeated large hemorrhages from the abscess cavity, and the lingula process was excised through an anterolateral approach.

**OPERATIVE TECHNIC**—The lingula is usually resected at the time the lower

lobe is removed and is readily accessible through the usual posterior incision. In the few instances in which the lingula alone has been resected, an antero-lateral approach, similar to that employed for a middle lobe lobectomy, has been found satisfactory.

It has been considered advisable to complete the lower lobe lobectomy, including closure of the hilar stump, before dealing with the lingula. Then the tip of the lingula is grasped with lung forceps and as adhesions that may be present are severed, it is drawn sharply upward and laterally, throwing the "frenum" into prominence. Adhesions to the pericardium in the line of the pericardiophrenic vessels may be troublesome, and at times the phrenic

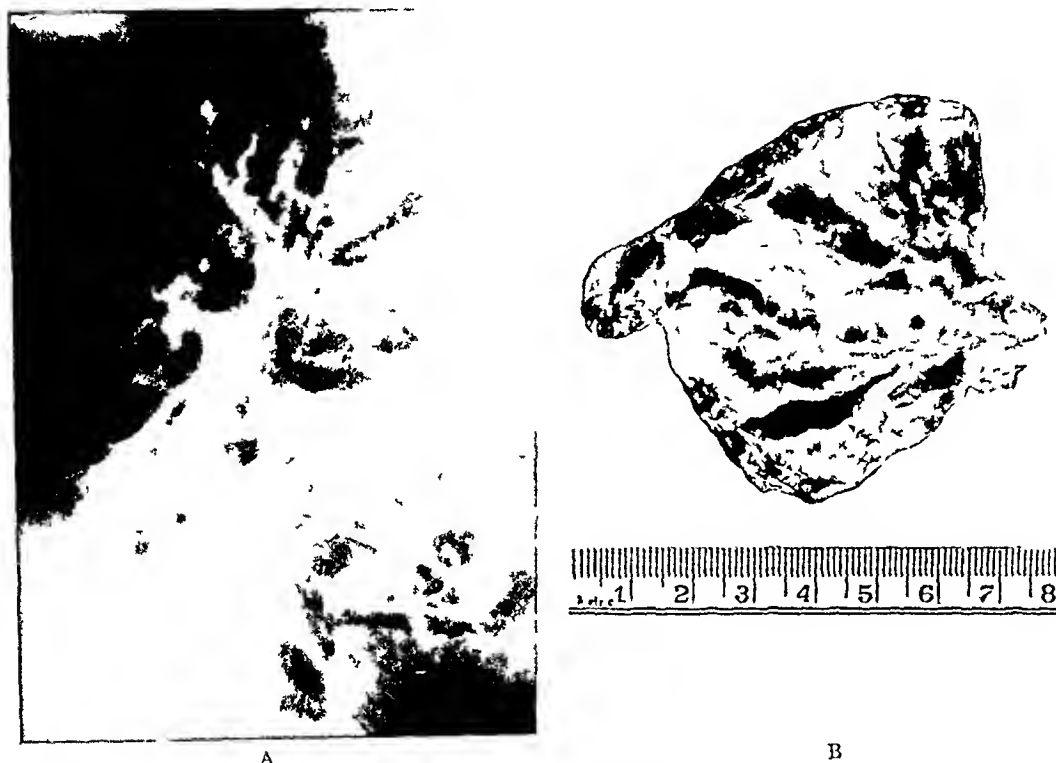


FIG 18—Postlobectomy bronchogram revealing residual bronchiectasis in the lingula two years after left lower lobectomy for bronchiectasis. (A) Left lateral view. Note how the lingula has been displaced downward and backward. Some of the shadow cast by the lipiodol is undoubtedly cast by the stump which was carefully surveyed at the secondary operation and found to be a contracted nodule of scar tissue at the hilum. (B) Resected lingula.

nerve is jeopardized as it tends to separate from the pericardium by traction on the adhesions.

Dissection into the hilar region is started at the base of the frenum, separating the lung parenchyma from the mediastinal pleura until the bronchus and its related blood vessels are exposed (Fig 20). The vessels are divided between ligatures, taking pains to avoid injuring the artery to the lower lobe in case the lower lobe has not been removed.

The anesthetist is then instructed to release the positive intratracheal pressure, allowing the upper lobe to deflate. A light clamp is applied to the bronchus with sufficient pressure to occlude its lumen but not crush the walls. The lobe is now re-inflated by restoring the positive intratracheal pres-

sue The lingula bronchopulmonary segment remains atelectatic (Fig 21) This maneuver not only positively identifies the bronchus but delineates the relatively avascular cleavage plane for section of the lung parenchyma

Division of the lung is now made with the aid of curved clamps placed in the form of a T, the vertical line paralleling the course of the "frenum" and stopping at the bronchus which is now amputated The plane between inflated and deflated alveoli is always discernible and the clamps are placed just on the atelectatic side to allow greater freedom in suturing Running stitch ligatures are then placed on the lung substance held by the clamps The bronchus is closed by a circular ligature, or simple plastic procedure, and adjacent lung tissue is drawn over the stump Finally, a running suture



FIG 19—Chronic lung abscess of the anterolateral segment of the lingula, and secondary bronchiectasis in the posteromedial segment (A) Anterolateral view after injection of lipiodol through the chronic chest wall sinus (B) The lingula after removal, showing the abscess cavity, and the cylindric bronchiectasis in the adjacent bronchi

on an atraumatic needle buries the hemostatic sutures and brings visceral pleurae together in a neat T-shaped line Lobules closely adjacent to the suture line may become filled with blood, but on the whole the procedure is attended by very little hemorrhage if the segmental vessels have been properly secured and the avascular cleavage plane followed If the ligature has been placed only on the posteromedial division of the artery, as may be done by mistake, brisk hemorrhage will be encountered from the anterolateral division as the hilum is approached

The anesthetist should now vary the intratracheal pressure allowing the

remaining portion of the upper lobe to deflate and inflate, thus demonstrating the integrity of the remaining bronchial divisions

If preoperative bronchograms have clearly demonstrated a normal antero-lateral division of the lingula bronchus, only the posteromedial segment need be resected. To this purpose the lung parenchyma is divided between clamps at the base of the "frenum" without exposing the structures at the hilum. The bronchus may be identified by palpation and a stitch ligature thrown about it. Adjacent vessels are clamped and ligated and bleeding from the lung parenchyma controlled with curved clamps as described above. As this dissection does not follow an avascular cleavage plane, it is attended by more



FIG 20—Dissection of the hilum of the lingula, as approached anteriorly with the tip of the lingula elevated. The bronchus lies in the center with the vein at its medial aspect and the artery situated laterally.

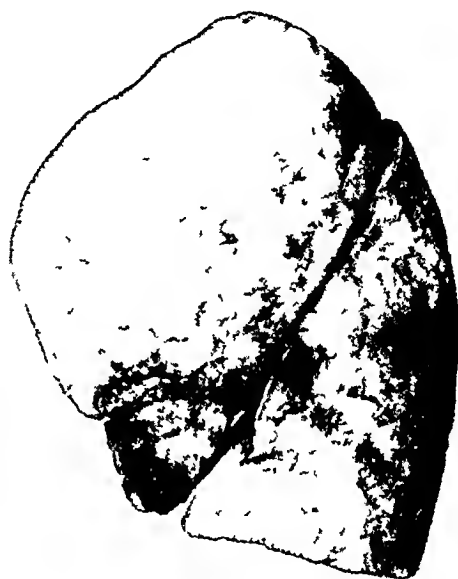


FIG 21—Appearance of normal lung inflated after obstruction of the lingula bronchus. The line of demarcation between the atelectatic lingula and the aerated upper lobe is clearly discernible.

bleeding, but if the dissection is carried from the hilum outward, it may be reduced to a minimum. Figure 22 demonstrates a posteromedial segment of the lingula bronchus removed by this method. Figure 23 is worthy of note in this connection. It has already been stated that involvement of the posteromedial division alone appears to be the commonest lesion of the lingula.

*Discussion*—Anyone with much experience in the surgery of bronchiectasis will realize that in many cases dense adhesions and active infection producing the so-called "frozen hilum" will make the dissection of hilum structures exceedingly hazardous or impossible. Interlobar fissures may be so fused that they cannot be identified. However, as less severe cases of the disease present themselves for surgical treatment, refinements of technic may be directed toward the conservation of normal lung tissue. This is particularly important if involvement of the contralateral lung indicates a program of bilateral operations.

The dorsal segment of the lower lobe is found free of disease in a con-

siderable number of cases of lower lobe bronchiectasis. Employing the principles described above for resection of the lingula, the lower lobe has been divided in two cases, preserving the large dorsal segment with its bronchus and vascular supply intact. In both of these patients the lingula was resected at the same time. The same deflation technic was employed to delineate the avascular plane for section of the lower lobe.



FIG 22—Posteromedial segment of the lingula process following excision for bronchiectasis

In one instance (Hosp No 18196) a patient was found sputum-free with healed fistula and incision two months after the operation (removal of left lower lobe and lingula). At the end of the third month, following a severe upper respiratory infection, an abscess developed in the left upper lobe requiring drainage and establishing large bronchial fistulae that will require plastic closure. This complication may or may not be attributable to the lingula resection, or may be due to the fact that only the posteromedial division was removed, leaving residual bronchiectasis in the anterolateral segment.

One very definite complication appears to attend the removal of a single bronchial segment that is not as frequent when an entire lobe is removed by the tourniquet technic. It has appeared in a high percentage of middle lobe lobectomies. The amputation of a large bronchus close to the main stem of the bronchial tree appears to favor obstructive atelectasis in closely adjacent areas of lung. After a middle

*Postoperative Complications*—It has already been stated that the lingula has been resected with the left lower lobe in 44 cases. It has also been resected without removal of the lower lobe in one instance, and at a period subsequent to lower lobe lobectomy in one instance. There have been no deaths in this series. Bronchial fistulae have closed spontaneously with the exception noted below.



FIG 23—Lipiodol injection through the chest wall sinus after removal of the left lower lobe and the posteromedial segment of the lingula demonstrating a residual empyema pocket communicating with the bronchial tree through a fistula. The lipiodol injection of the bronchus is

normal

lobe lobectomy, complete or partial atelectasis of the lower lobe may persist for a period of three to four weeks. It is attended by cough and mucoid sputum that subsides as the lobe reexpands. The same happening has been observed in the upper lobe following complete resection of the lingula but does not often appear if the posteromedial division alone is resected. It has also occurred in the dorsal segment of the lower lobe after resection of the inferior segment.

This is not a surprising event and is readily explained by the inflammatory edema that must surround the focus of secondary healing in the bronchial tree. To minimize this complication, trauma is to be avoided in closing the bronchus and fine absorbable suture material employed. In a one stage operation in a free pleural cavity particular attention is to be paid to postoperative expansion of the lung.

Just how important this complication will be as a hazard of segmental resection of the lung remains to be seen. The advantage of a smaller residual empyema pocket when healthy lung is conserved is to be balanced against it.

#### SUMMARY

The anatomy of the lingula segment of the left upper lobe is considered. The lingula bronchus and blood vessels are described.

The bronchogram of this particular segment is illustrated.

Indications for surgical removal of the lingula are discussed and operative technics described.

More general applications of the principle of segmental pneumonectomy are indicated, particularly with reference to the lower lobes.

It is suggested that the bronchopulmonary segment may replace the lobe as the surgical unit of the lung.

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# THE GRADING AND PROGNOSIS OF CARCINOMA OF THE COLON AND RECTUM

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SINCE 1893, when Von Hansemann<sup>1</sup> first attempted to grade the malignancy of tumors by their histology, many pathologists have made similar studies on all varieties of tumors. Most have agreed that grading is of some value in prognosis, but have disagreed as to how much. Others have not found it of any significance. Studies on colon and rectal tumors have been made chiefly by Rankin and Broders,<sup>2</sup> Rankin,<sup>3</sup> Rankin and Olson,<sup>4</sup> Dukes,<sup>5, 6</sup> Stewart and Spies,<sup>7</sup> Wood and Wilkie,<sup>8</sup> and Raiford.<sup>9</sup> Each was convinced of the importance of grading in prognosis, but did not always use the same method. Rankin and Broders divided the tumors into four grades according to the relative proportion of differentiated and undifferentiated cells. Dukes used this method also. Stewart and Spies based their grades on the number of mitoses, the amount of papillary formation, the degree to which the polarity of the cells and their nuclei had been maintained and the preservation of adenoid structure. Wood and Wilkie adopted a similar method, based mainly on low power magnification, but apparently did not use the frequency of mitosis as a criterion. MacCarty<sup>10</sup> advocated other criteria, based on changes in the stroma, such as lymphocytic infiltration, fibrosis, and hyalinization. Other pathologists have used still other methods for estimating the malignancy of tumors. In a recent study of a series of carcinomata of the breast, Haagensen<sup>11</sup> has, for the first time, attempted to determine statistically the value of the various criteria used. Fifteen in all were studied, involving differences in the growth of cells, differences in cell morphology, and differences in the reaction of the stroma. Six were found to have prognostic significance and were used to determine the grades of the tumors in his series. These criteria were the papillary structure, comedo character, adenoid arrangement, variations in size and shape of the nuclei, the number of mitoses, and gelatinous degeneration. Of course, criteria which are of value in breast cancer are not necessarily suitable to apply to other types. In each type of tumor, they should be redetermined by such a study as Haagensen has made. In the present series, this has been attempted.

This series includes all the cases of carcinoma of the colon and rectum admitted to the Presbyterian Hospital from 1916 to 1932, inclusive, upon whom a resection had been performed with the expectancy of possible cure of the patient and in which cases microscopic sections were available. Both

the colon and rectal tumors were studied together, as their pathology is essentially the same. Cases treated by palliative operations were not included. In the right colon, the operations were all ileocolic resections. In the left colon, which included the sigmoid, various types of resections, many of the Mikulicz type, were used. In the rectum and rectosigmoid, the operations included resections, perineal proctectomies and abdominoperineal operations in one or more stages.

The 225 tumors in the series were about equally divided between the colon and rectum. Of the 114 colon carcinomata, 20 per cent were found in the cecum, ascending colon, and hepatic flexure, 23 per cent in the transverse colon, 15 per cent in the splenic flexure and descending colon, and 42 per cent in the sigmoid. The low total for the cecum, ascending colon, and hepatic flexure and the high figure for the sigmoid are somewhat unusual. In eight of the 19 cecum and ascending colon cases, in which the origin of the tumor could be determined, it began at the medial and posterior wall of the gut. Craig and MacCarty<sup>12</sup> have emphasized the frequency of this site of origin. All eight of the cecal growths and one of the ascending colon showed involvement of the ileocecal valve. Craig and MacCarty found it involved in 64 per cent of 100 cancers of the cecum.

There were 223 cases operated upon. Of these, 18 were lost to follow-up, 59 were classed as operative deaths, nine died from other causes without evidence of recurrent disease, and 11 were without adequate microscopic sections. The remaining 126 cases were alive five years after operation, with or without disease, or died within five years from the disease.

In judging the criteria for grading, only five-year survivals, with or without disease, and those dead from the disease within five years, were considered. The operative deaths, those lost to follow-up, and those dead from other causes were not included. A better basis of comparison is possible when these cases have been excluded. In estimating the results of surgical treatment, however, or when one type of therapy is to be compared with another, these cases should be included. This point has been especially emphasized by the Cancer Commission of the League of Nations.<sup>13</sup> The results were expressed by both the percentage of five-year survivors after operation and of those alive over five years without evidence of disease. As there were only seven cases surviving over five years that had recurrences out of 68 five-year survivors, or about 10 per cent, the two sets of figures run fairly parallel. Two of these patients lived for eight years after operation before succumbing to the disease. Many patients were followed much longer than five years. The longest follow-up was 20 years. Follow-up results were based on actual examination of the patient in nearly every case. In the whole series of cases, the five-year follow-up was 92 per cent complete. In the cases considered for judging the criteria and the grades of malignancy, it was 100 per cent.

THE CRITERIA FOR GRADING—Guided largely by the experience of Haagensen in grading breast tumors, eight criteria were selected as most promising for study. They can be grouped as he has suggested according to the manner

of growth of the cells, the cell morphology, and the reaction of the stroma. None of those chosen for study belonged to the last group. Those based on the manner of growth of the cells were the papillary character, glandular arrangement, invasiveness, nuclear polarity, and extracellular "mucin" secretion. Those based on differences in cell morphology were the size of nuclei, the variation in size of nuclei, and the number of mitoses.

There is, perhaps, a slight amount of overlapping between some of these criteria. Invasiveness and loss in glandular arrangement, for example, may represent a somewhat similar histologic picture, yet they are not necessarily the same.

Microscopic sections were nearly always available from several regions



FIG 1.—Carcinoma of the colon with marbled papillary structure (X33)

of the tumor. In most cases, these were stained with hematoxylin and eosin. In the more recent cases, Masson's anilin blue trichrome stain was also made. The mucicarmine stain for the presence of mucin, or more strictly speaking, mucicarminophilic substance, was used in about 52 per cent of cases.

*Papillary Character*—Papillary structure is one of the outstanding features of the benign adenomata, and its presence in a malignant growth is usually taken as evidence of greater differentiation. Stewart and Spies have emphasized this point. Table I, however, shows only a slightly better follow-up result in cases in which papillary character was present. The chief disadvantage of this criterion is that it is usually present only in the superficial portions of the tumor and is replaced by the more typical glandular structure in the deeper layers. Sections taken through the surface of a tumor which has undergone considerable ulceration may fail completely to show this characteristic. It was, therefore, felt to be unreliable for prognosis.

# GRADING AND PROGNOSIS OF CARCINOMA

TABLE I  
PAPILLARY CHARACTERS

		<i>Present</i>	<i>Absent</i>
Cases	126	67	59
Five-year survivors			
Cases	68	42	26
Per cent	54%	63%	44%
Five-year survivors without evidence of disease			
Cases	61	38	23
Per cent	48%	57%	39%

*Glandular Arrangement*—The tendency to form fairly regular tubules is a well recognized feature of an adenocarcinoma of low grade malignancy. The fact that in most cases in this series this characteristic was well marked



FIG 2—Carcinoma of the colon with marked adenoid arrangement of the cells (X85)

supports the accepted view that carcinomata of the colon and rectum are in general relatively well differentiated. On the other hand, its absence in only a few cases limited its usefulness as a yardstick for grading. It proved, however, to be of value



FIG 3—Carcinoma of the rectum with moderate adenoid arrangement of the cells (X85)

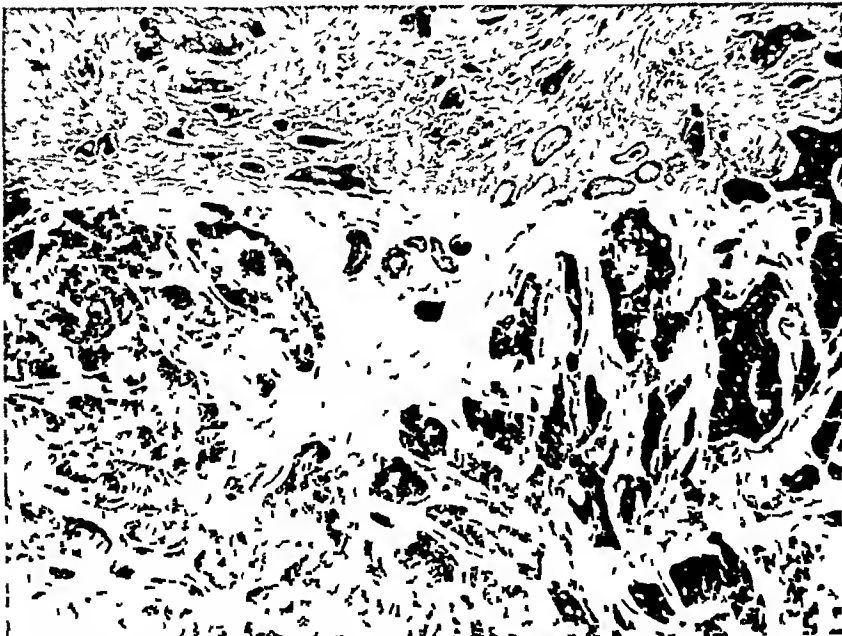


FIG 4—Carcinoma of the colon with slight adenoid arrangement of the cells (X85)

# GRADING AND PROGNOSIS OF CARCINOMA

TABLE II  
GLANDULAR ARRANGEMENT

		<i>Marked</i>	<i>Moderate</i>	<i>Slight or Absent</i>
Cases	126	91	24	11
Five-year survivors				
Cases	68	56	9	3
Per cent	54%	62%	38%	27%
Five-year survivors without evidence of disease				
Cases	61	50	8	3
Per cent	48%	55%	33%	27%

*Invasiveness*—This term was used to describe the tendency of tumor cells to appear to stream out singly or in small groups into the surrounding tissues. The basic adenoid structure may or may not have been lost. From the results, this criterion had greater prognostic value than any other.

*Loss of Nuclear Polarity*—The term “nuclear polarity” is used here to describe the basal position of the nuclei in relation to the basement membrane of the gland tubule, rather than to their position in the cells. In the more differentiated tumors, the polarity of the nuclei is well preserved. Both the nuclei and the cells are arranged in several layers with the nuclei toward the basement membrane, and an outer clear zone of cytoplasm near the lumen. In the less differentiated tumors, the number of nuclear layers increases. The nuclei no longer maintain their basal position but may lie anywhere in the

TABLE III  
INVASIVENESS

		<i>Slight</i>	<i>Moderate</i>	<i>Marked</i>
Cases	126	45	33	48
Five-year survivors				
Cases	68	36	19	13
Per cent	54%	80%	56%	27%
Five-year survivors without evidence of disease				
Cases	61	32	18	11
Per cent	48%	71%	55%	23%

gland wall, invading the cytoplasmic zone toward the lumen. Whether this change is due to the increase in the number of cell layers, to the loss of polarity of the nucleus within the cell, or to both, is not always apparent. The results showed this test to be of some significance.

*“Mucin” Secretion*—The presence of varying amounts of “mucin” is of common occurrence in large bowel tumors. Broders,<sup>14</sup> Ochsenshirt<sup>15</sup> Rankin and Chumley,<sup>16</sup> and Parham<sup>17</sup> maintain that it is a product of secretion. They believe that the ability to secrete can be taken as a test of cellular differentiation, and that usually the greater the secretion the less the malignancy of the



FIG 5—Carcinoma of the rectum showing very slight invasiveness. The tumor cells have not penetrated the muscularis mucosae (X85)

tumor Miles<sup>18</sup> and Boyd<sup>19</sup> consider it to be a degenerative change. Raiford<sup>20</sup> believes that the mucoid substance is due to oversecretion in the signet-ring



FIG 6—Carcinoma of the colon showing moderate invasiveness (X85)

cell type of tumor, and to degeneration in the other "mucoid" tumors. In this study, the amount of the substance was judged by the amount in the lumen of the acini and in the tissues outside. Large lakes of "mucin" were frequently

seen scattered through the stroma. One criticism of this criterion is that much of this excess "mucin" may be the result of mechanical difficulties in drainage through the acini rather than to overproduction. Estimation of the amount of



FIG. 7—Carcinoma of the colon showing marked invasiveness (X33)

intracellular "mucin" is difficult and was not attempted. However, when it appeared in the cells to the extent of crowding the nucleus to one side to

TABLE IV  
LOSS OF NUCLEAR POLARITY

		<i>Slight</i>	<i>Moderate</i>	<i>Marked</i>
Cases	126	45	59	22
Five-year survivors				
Cases	68	33	28	7
Per cent	54%	72%	47%	28%
Five-year survivors without evidence of disease				
Cases	61	28	27	6
Per cent	48%	62%	46%	27%



give the characteristic appearance of the signet-ring type of tumor, it was carefully noted

There were 15 cases classed as "mucoid" or "colloid" tumors with follow-ups suitable for grading. In these cases, the "colloid" substance occupied



FIG 8—Carcinoma of the colon with slight loss in polarity of the cell nuclei ( $\times 200$ )

large areas of the tumor, sometimes to such a degree that the epithelial elements were difficult to find. The difference is apparently mainly one of degree. The excess "colloid" can even be recognized in the gross specimen. Seven of the 15 cases were of the signet-ring cell type. Most pathologists regard them as a particularly malignant group and often class them separately. Just how these two types should be grouped is still an undecided question. The distinction between them is not always clear-cut. Intermediate types are not infrequent. They may occupy scattered areas in a tumor which presents, in its other portions, a typical adenomatous structure without excess "colloid." They may be associated with each other so that "colloid" areas with well differ-

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entiated glands mingle with signet-ring cells which have usually lost their glandular arrangement. Classification in these cases is difficult



Fig 9—Carcinoma of the colon with moderate loss in polarity of the cell nuclei ( $\times 200$ )

Our follow-up results with reference to the "mucin" content of the tumors were quite inconclusive, irrespective of whether the signet-ring group was included or not. This criterion was, therefore, not used in grading.

TABLE V  
EXTRACELLULAR "MUCOID" MATERIAL  
Signet-Ring Cells Included

	126	<i>Slight</i> 94	<i>Moderate</i> 15	<i>Marked</i> 17
Cases				
Five-year survivors	68	50	9	9
Cases	54%	53%	60%	53%
Per cent				
Five-year survivors without evidence of disease	61	45	8	8
Cases	48%	48%	53%	47%
Per cent				

*Size of Nuclei and Variation in Size of Nuclei*—The average size of the nuclei and the variation in size of the nuclei were discarded as reliable criteria

because of the difficulty in getting accurate measurements and of getting an accurate average figure for the nuclear diameter, even with the help of an



FIG 10—Carcinoma of the colon with marked loss in polarity of the cell nuclei (X200)

eye-piece micrometer. Variations in fixing and staining technic also tend to make this method unreliable.

TABLE VI

NUMBER OF MITOSES

		<i>Few</i> (Less than 1)	<i>Moderate</i> (1 or 2)	<i>Numerous</i> (Over 2)
Cases	126	19	70	37
Five-year survivors				
Cases	68	15	36	17
Per cent	54%	79%	51%	46%
Five-year survivors without evidence of disease				
Cases	61	14	32	15
Per cent	48%	74%	46%	41%

*Number of Mitoses*—The frequency of mitoses has always been considered one of the best means of judging the cellular activity of a tumor

It was accepted for purposes of grading although the results were not particularly convincing. It is realized that of all the criteria adopted this one lends itself most of all to technical errors because of variations in staining and fixing technic. It was the least convincing of the criteria chosen.

The above results, obtained in testing the various criteria, were nearly



FIG. 11.—'Mucoid' or 'colloid' carcinoma of the rectum not of the signet ring cell type (X200)

the same, whether computed separately for the right colon, left colon, rectum, or for all combined.

**METHOD OF GRADING**—Three grades of malignancy were adopted for this series of cases instead of four as used by Broders,<sup>14</sup> and Stewart and Spies.<sup>7</sup> We agree with Haagensen that, in the present state of our knowledge, the interpretation of differences in histologic structure is not sufficiently accurate to warrant more than a very simple classification.

On the basis of the results, four histologic criteria were chosen for grading. They were the invasive tendency, glandular arrangement, nuclear polarity, and frequency of mitoses.

As shown in the preceding tables, each criterion was subdivided into three groups. In order to work out a tentative numerical method of grading, each group was rated one, two, or three points, according to the degree the characteristic was present. The lowest possible total for a tumor judged by these four criteria was, therefore, four, and the highest, 12. The three grades were then arbitrarily divided according to points as follows: Grade I, 4-6 points (inclusive), Grade II, 7-8 points (inclusive), and Grade III, 9 points and



FIG 12 — 'Mucoid' or 'colloid' carcinoma of the colon of the signet ring cell type (X33)

over. This method has been referred to in a later table as the numerical method of grading.

There are several objections to such a method. It tends to become too rigid and complicated. The attempt at mathematical accuracy is out of proportion to our ability to rate histologic characteristics correctly. Moreover, it places an equal value on each criterion which is probably incorrect. Realizing the shortcomings of such a method, the cases were also graded on the basis of these four criteria but without any attempt at numerical evaluation.

# GRADING AND PROGNOSIS OF CARCINOMA

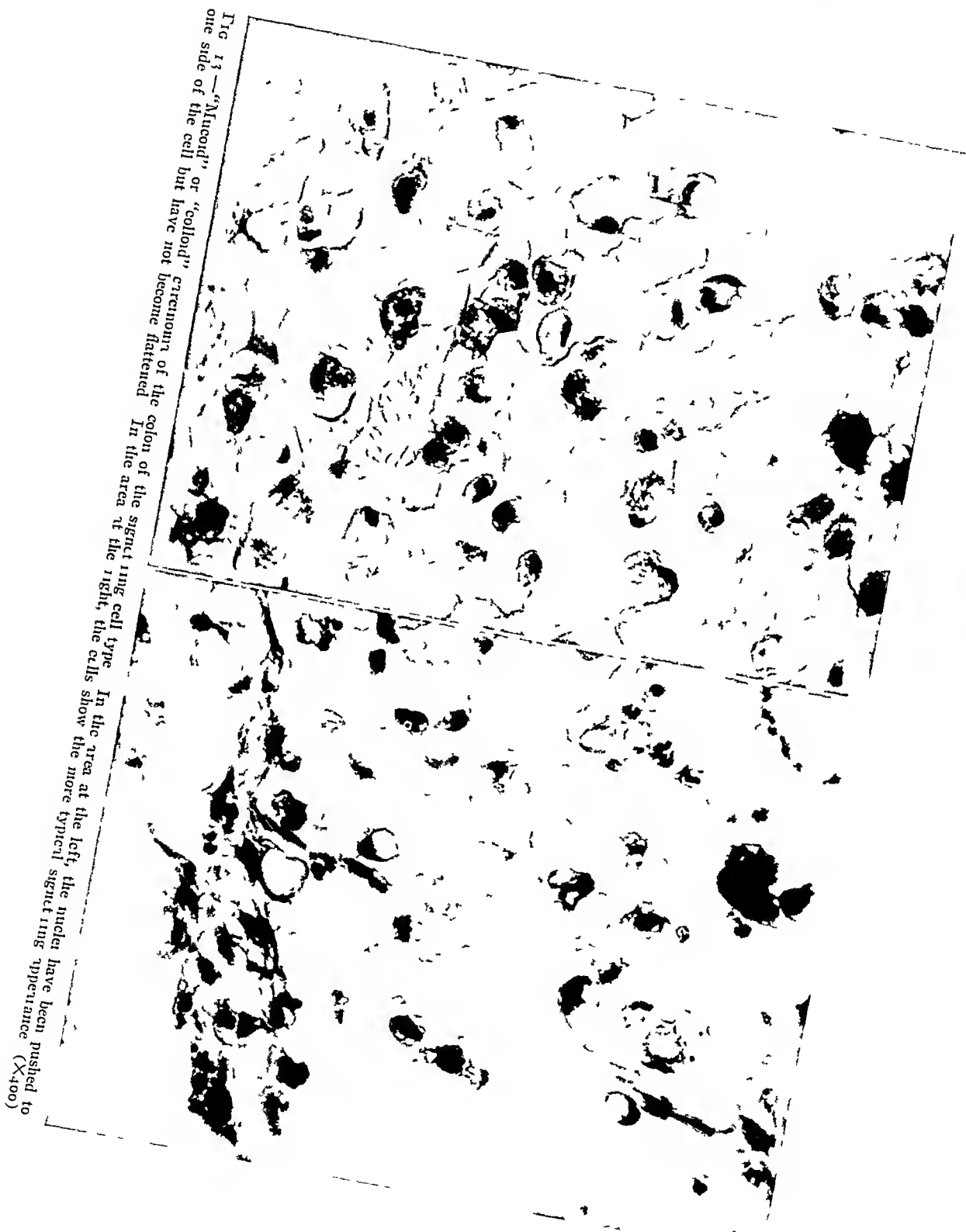


Fig. 13—"Mucoid", or "colloid", carcinoma of the colon of the signet ring cell type. In the area at the left, the nuclei have been pushed to one side of the cell but have not become flattened. In the area at the right, the cells show the more typical signet ring appearance (X400)

This method has been referred to in a later table as the nonnumerical method. It may increase the human factor in grading, but has the advantage of simplicity and gives the pathologist more leeway in judging the relative importance of the criteria. It was noted that with this method the tendency was to put greater emphasis on the manner of growth of the tumor, especially as to invasiveness, than on the frequency of mitoses. That such an emphasis may be warranted is suggested by the fact that invasiveness was shown by follow-up results to be apparently of more value in prognosis than any of the other



FIG. 14—Carcinoma of the colon, Grade I (X85)

criteria. Grading was estimated mainly with the low power magnification (x80), except in determining the frequency of mitoses. In comparing the grades adopted under these two methods, surprisingly little difference was found. Accordingly, the simpler nonnumerical method was chosen as preferable and has been used throughout this analysis. Whichever method is used, the general characteristics of a tumor belonging to each grade is the same.

**Grade I**—Tumors of this grade show a well differentiated, compact glandular structure. The acini are lined with two or three layers of cells whose nuclei tend to remain close to the basal layer of the gland, leaving a clear zone near the lumen. There is little tendency of individual cells or small

groups of cells to push out into the surrounding tissue. Mitoses are infrequent. Although our results did not give definite data on papillary structure, we believe many tumors in this grade show a close resemblance to the benign adenoma.

Grade II—In this grade, the glandular arrangement is still preserved. Some glands, however, appear to be loosely and irregularly arranged. Their walls are thicker and are composed of cells in three or more layers with their



FIG. 15—Carcinoma of the colon, Grade II (X85)

nuclei scattered throughout the wall of the gland. The central clear zone in the cytoplasm of the cells about the lumen is largely lost. A tendency of the cells to stray off into the tissues can be seen, especially at the deep advancing edge of the tumor. Mitoses are more numerous.

Grade III—The glandular structure may be completely or nearly completely lost. Parts of the growth, at least, may show tumor cells growing in solid masses or cords with little tendency to arrange themselves around a central lumen. Individual cells or small clumps may be seen streaming out irregularly into the tissues. This is again usually most marked at the deep edge of the tumor. Nearly all cell polarity is lost. Mitoses are frequent.

When the tumor shows considerable morphologic variations in different



areas, and this was not infrequent, grading may be difficult. In this event, the grade of the tumor was taken as that of the least differentiated area.

"Mucoid" or "colloid" tumors, whether of the signet-ring cell type or not, were graded by the same criteria as the other tumors, and were not arbitrarily placed in any one grade.



FIG. 16—Carcinoma of the colon Grade III (X85)

**DISTRIBUTION OF CASES IN GRADES**—The distribution of cases in the three grades showed that most were in Grade I and Grade II, emphasizing the relatively good differentiation of most of these tumors. The proportion of cases in the grades was approximately the same, whether calculated only for the five-year survivors with or without the disease and those dead from recurrences, or for the entire group irrespective of follow-up results. The latter group is shown in Table VII because of its larger size. The distribution in the colon and rectum was similar but showed several marked differences. The incidence of Grade I cases was 19 per cent higher, and that of Grade III cases 16 per cent lower, in the colon than in the rectum, suggesting that colon tumors tend to be better differentiated.

There were 27 "mucoid" or "colloid" tumors, 13 per cent of the whole series. The incidence was about the same in the right and left colon and rectum. Rankin and Chumley found an incidence of 4.9 per cent, and Parham

# GRADING AND PROGNOSIS OF CARCINOMA

of 16 per cent, in the colon and rectum combined. Ten of the 27 cases were of the signet-ring type, and 17 were not. When the 17 "colloid" cases, exclusive of the signet-ring type, were studied separately, they were found to show by far the greater proportion of cases in Grade I, with a 21 per cent higher figure than that for the whole series. All but two of the 10 signet-ring tumors, on the other hand, were in Grade III, with none in Grade I. Ochsenhirt,

TABLE VII  
DISTRIBUTION OF CASES ACCORDING TO GRADE

	Grade I	Grade II	Grade III
Right colon			
Cases	12	11	5
Per cent	43%	39%	18%
Left colon			
Cases	40	26	12
Per cent	51%	33%	15%
Right and left colon			
Cases	52	37	17
Per cent	49%	35%	16%
Rectum			
Cases	33	42	35
Per cent	30%	38%	32%
Colon and rectum			
Cases	85	79	52
Per cent	39%	37%	24%

Raiford, Wood and Wilkie, and Rankin and Chumley had similar findings and stressed the greater malignancy of the signet-ring tumors. It should be emphasized again that grading "colloid" tumors was often difficult because of the scarcity of epithelial cells. Most of the signet-ring cases were in the rectum and most of the other "colloid" cases in the colon.

TABLE VIII  
FOLLOW-UP RESULTS ACCORDING TO GRADE  
*Nonnumerical and Numerical Methods*

		Grade I		Grade II		Grade III	
		Nonnu- merical	Numeri- cal	Nonnu- merical	Numeri- cal	Nonnu- merical	Numeri- cal
Cases	126	46	50	45	40	35	36
Five-year survivors							
Cases	68	37	38	21	19	10	11
Per cent	54%	80%	76%	47%	48%	29%	31%
Five-year survivors without evidence of disease							
Cases	61	32	33	21	19	8	9
Per cent	48%	70%	66%	47%	48%	23%	25%

**FOLLOW-UP RESULTS ACCORDING TO GRADE**—The follow-up results showed a marked difference in the chances of survival in the three grades. The incidence of Grade I cases surviving operation for five years without evidence of the disease was over three times that of the Grade III cases, and 23 per cent more than for the Grade II cases. The correlation between grades and survival was about the same in both the colon and rectum. It should be reemphasized that these results are based only on five-year survivals with or without disease, and those dead from recurrences. Operative deaths and those dying from other causes have not been included here. The results by both the nonnumerical and numerical methods are given below. As we have already explained, they were nearly the same in each case. The nonnumerical method was adopted because of greater simplicity.

The value of grading was then studied in the cases without and with metastases in the lymph nodes. As would be expected, the cases without node involvement gave much better results than those with involvement. The influence of the grades on the results was shown in both groups. It appeared to be greater in cases with node involvement, although this group is presumably more affected by the extent of the disease at the time of operation. Rankin and Olson found that the grades influenced prognosis about equally in both these groups.

TABLE IX  
FOLLOW-UP RESULTS ACCORDING TO GRADE  
*In Cases With and Without Lymph Node Metastases*

	Grade I		Grade II		Grade III	
	Node Metastases Absent	Node Metastases Present	Node Metastases Absent	Node Metastases Present	Node Metastases Absent	Node Metastases Present
Cases	44	2	29	16	13	22
Five-year survivors						
Cases	36	1	15	6	8	2
Per cent	82%	50%	52%	37%	62%	9%
Five-year survivors without evidence of disease						
Cases	31	1	15	6	6	2
Per cent	70%	50%	52%	37%	46%	9%

The relationship between the grade of the tumor and the incidence of node metastases was also studied and is shown in the following table. Grade III cases had an incidence nine times greater than Grade I. Rankin and Olson, and Wood and Wilkie had similar findings.

TABLE X  
INCIDENCE OF NODE METASTASES ACCORDING TO THE GRADE

	Grade I	Grade II	Grade III
Cases	85	79	52
Cases with node metastases	5	25	28
Per cent of cases with node metastases	6%	32%	54%

As grading is primarily a measure of the rapidity of growth, its influence should be seen in comparing the duration of life after operation in those dying with recurrences. Grade I cases had an average postoperative life of 34 months, as compared to 22 months in both Grades II and III, a difference of just a year. No difference was found between the Grade II and III cases. The number of cases, however, is too small to warrant definite conclusions.

**DUKES' METHOD OF PROGNOSIS ACCORDING TO THE EXTENT OF SPREAD —** From the previous tables it would seem evident that the grade of a tumor is a determining factor in the patient's prognosis. There is, however, another factor of even greater importance, and that is the extent of spread of the tumor. Obviously, the knowledge that a tumor was incompletely removed at operation or that it proved to be confined to the mucosal layer is of greater prognostic value to the surgeon in any specific case than its histologic characteristics. Dukes<sup>5</sup> has adopted a classification based on the extent of spread which should be studied before the relative merits of the two methods can be judged.

Dukes divided cancers of the rectum into three groups A, B, and C. (A) Cases in which the growth was confined to the wall of the rectum. (B) Cases which had spread by direct continuity to the extrarectal tissues but had not reached the regional lymph nodes. (C) Cases which had metastases in the regional nodes. He showed that lymphatic metastases rarely occurred until the growth had penetrated the muscle layers into the extrarectal tissues and become a B case. None of his cases with the tumor limited to the rectal wall had node involvement. Miles<sup>21</sup> has reported several exceptions to this rule, and Wood and Wilkie<sup>8</sup> had two out of 100 rectal carcinomata studied, but they are apparently very rare.

The classification of our colon and rectal cases by Dukes' method showed that the greater number were B cases, with a smaller, but nearly equal, number of A and C cases. The percentage of advanced C cases in the rectum was

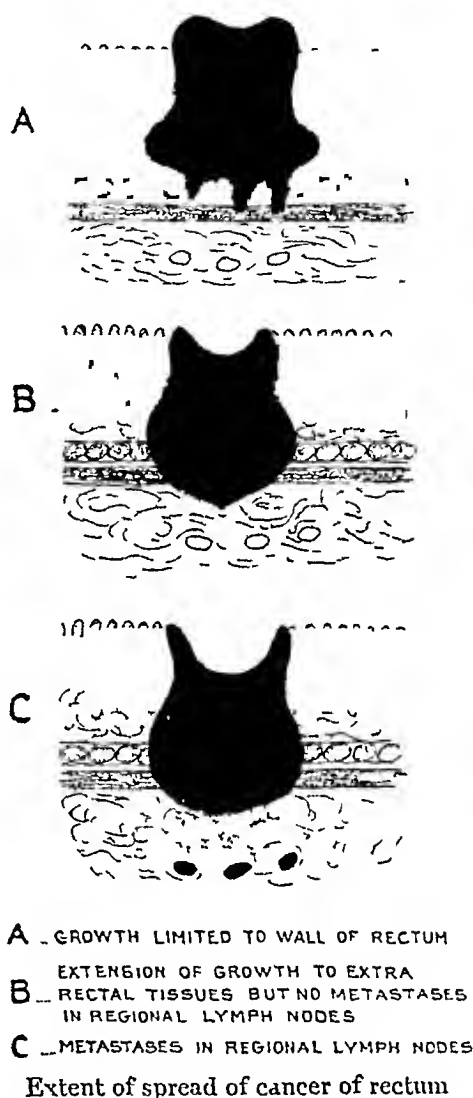


FIG. 17 — Dukes' classification of carcinoma of the rectum (after Dukes)

twice as great as in the colon. Conversely, there was only 18 per cent of the rectal tumors in the A group, as compared to 34 per cent of the colon tumors. The proportion of tumors in an early A stage was especially high in the right colon, 44 per cent. Apparently, cancers of the rectum were operated upon at a later stage in their development than those in the colon. Whether this difference was due to the more rapid spread of the rectal growths, to delay in operation, or to the late development of symptoms in these cases was not determined. A comparison of our rectal cases with the series reported by Dukes showed a similar distribution except for a 10 per cent higher proportion of C cases in his series. This difference may be due to the fact that in our earlier cases the gross and microscopic examination of the lymph nodes was less carefully made than in our later cases, and was sometimes inadequate.

TABLE XI

## DISTRIBUTION OF CASES ACCORDING TO DUKES' CLASSIFICATION

	A	B	C
Right colon			
Cases	12	11	4
Per cent	44%	41%	15%
Left colon			
Cases	24	40	14
Per cent	31%	51%	18%
Right and left colon			
Cases	36	51	18
Per cent	34%	49%	17%
Rectum			
Cases	20	49	40
Per cent	18%	45%	37%
Colon and rectum			
Cases	56	100	58
Per cent	26%	47%	27%

Our series has upheld Dukes' contention that extension of the tumor through the rectal wall is by continuity and that only when the tissues outside of the wall are reached do metastases to the nodes occur. Of 69 colon and rectum tumors with node metastases studied microscopically, only two showed the nodes involved before the smooth muscle layers of the bowel wall had been penetrated. Both were in the rectum. One of the cases was particularly unusual. The growth was limited entirely to the mucous layer of the bowel. At one point the muscularis mucosae appeared to be interrupted, but the submucosa was not invaded in the sections studied. One node, however, showed metastasis. There were four other cases which at first appeared to be exceptions to this rule, but which were later found to follow it after new sections had been made and studied. Our series has also shown that Dukes' generalization is true, except for rare exceptions, not only for the rectum but for the colon as well. Once the tumor had penetrated the muscle layers, however, and invaded the extrarectal tissues, node involvement was found in 26 per cent of the colon cases and 45 per cent of the rectal cases.

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If the 10 signet-ring tumors are taken separately, they all proved to be cases. On the other hand, the 17 other "colloid" cases showed about the same distribution in each group as did the whole series.

**THE VALUE OF DUKES' CLASSIFICATION IN PROGNOSIS**—The five-year follow-up showed strikingly different results in the A, B, and C cases. As in previous tables, they were based only on cases surviving operation five years with or without disease, and those dying from cancer within that period. The A, B, and C, groups had 100, 43, and 23 per cent five-year survivors, respectively, without evidence of disease in the colon and rectum combined. Thus, the chances of being alive over five years was over four times as good for the A as for the C cases. The results were approximately the same in the colon and rectum separately as in the combined group. No A case, definitely proven by gross and microscopic examination, has died after operation from the disease. There were several cases, however, which were difficult to classify as A or B cases because of inadequate sections. For proper accuracy, such a classification requires that sections be taken at the point of deepest penetration of the growth. Repeated sections may be necessary to determine whether or not it has spread beyond the bowel wall. Not all of our sections in the early cases completely met these requirements. These results are very similar to those reported by Dukes<sup>6</sup> for a series of 128 carcinomata of the rectum treated by perineal excision. He had 93, 65, and 23 per cent five-year survivors in the A, B, and C cases. Gordon-Watson<sup>22</sup> has suggested that the difference between the five-year survival rates of the A and B cases after operation may be partly explained by the greater liability of the B cases to spread by venous channels. He points out, however, that invasion of the veins with metastasis to the liver before the lymph nodes are involved is rare.

TABLE XII  
FOLLOW-UP RESULTS ACCORDING TO DUKES' CLASSIFICATION

		A	B	C
Cases	124	27	58	39
Five-year survivors				
Cases	68	27	32	9
Per cent	54%	100%	55%	23%
Five-year survivors without evidence of disease				
Cases	61	27	25	9
Per cent	49%	100%	43%	23%

The value of this classification in prognosis is obvious. It shows the great importance of determining the exact extent to which the bowel wall has been penetrated and whether or not the nodes contain metastases. The difference in survival in the three groups was even more clear-cut than that seen when the results in the three histologic grades were compared. It is unfortunate

that the B group with indeterminate prognosis was so large and contained 47 per cent of the cases

Before comparing the value of the two methods, however, the distribution of the A, B, and C cases in the three histologic grades, I, II, and III, should

TABLE XIII

DISTRIBUTION OF GRADES ACCORDING TO DUKES' CLASSIFICATION

	A	B	C
Grade I			
Cases	39	39	6
Per cent	46%	46%	7%
Grade II			
Cases	14	38	24
Per cent	19%	50%	31%
Grade III			
Cases	4	19	28
Per cent	8%	37%	55%

be studied Table XIII shows a definite relationship between the two classifications There is a high proportion of A cases in Grade I, and a very low proportion in Grade III, whereas the C cases with lymph node metastases are most numerous in Grade III and fewest in Grade I This relationship is seen in the colon and rectal group separately as well as in the combined group Dukes<sup>6</sup> found this same correlation between the two classifications in his series

Dukes has suggested that the apparent value of histologic grading is misleading He believes that much of its significance can be attributed to this distribution of early A cases in Grade I and of late C cases with node metastases in Grade III, rather than to the histology of the tumor itself But these differences in the limits of spread of the tumors in the grades must be due to differences in their rate of growth or, in other words, to the grade of malignancy The two classifications are closely related The extent of spread is based primarily on the activity and grade of the tumor It is more important than the grade in any individual case Unfortunately, it cannot always be determined with absolute accuracy If it could be so determined, the prognosis would be easy except in the C cases Nearly every A and B case would be assured of cure, and only the C cases would be left in doubt But the limits of growth can only be gauged approximately Errors are unavoidable Grading gives further information on which to estimate the probable extent of the tumor in both the early and late cases It is perhaps of most value when applied to a group of tumors As Dukes has remarked, it is essentially an index of the "pace of growth" The two methods should be used to supplement one another They give different kinds of information, both of which are helpful in prognosis

An attempt has been made to combine the two methods in a common classification The five-year results were studied in each of the nine possible combinations, as shown in Table XIV The classification is somewhat compli-

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cated but seems to show promise, as the results indicate. The Duke's rating is placed before that of the grade as it is the more important of the two. The number of cases is as yet too small to test the real value of the method in prognosis.

TABLE XIV

FOLLOW-UP RESULTS ACCORDING TO GRADE AND DUKES' CLASSIFICATION COMBINED

	<i>A1</i>	<i>A2</i>	<i>A3</i>	<i>B1</i>	<i>B2</i>	<i>B3</i>	<i>C1</i>	<i>C2</i>	<i>C3</i>
Cases	18	6	2	25	22	11	2	16	22
Five-year survivors									
Cases	18	6	2	18	9	6	0	6	3
Per cent	100%	100%	100%	72%	41%	55%	—	38%	14%
Five-year survivors without evidence of disease									
Cases	18	6	2	13	9	4	0	6	3
Per cent	100%	100%	100%	52%	41%	36%	—	38%	14

**LYMPH NODE METASTASES AND PROGNOSIS**—The presence or absence of lymph node metastases has often been used as a rough basis for prognosis. Such a method is somewhat similar to Duke's but less accurate. The incidence of node metastases has been shown to be 27 per cent for all the cases in the series. It was twice as high in the rectum as in the colon. This figure is probably considerably lower than it should be, as the earlier cases in the series were not examined as thoroughly as the more recent ones. In a recent carefully examined series of 100 rectal cases treated by perineal and perineoabdominal excision, Gabriel, Duke and Bussey<sup>23</sup> found node metastases in 62 per cent. Wood and Wilkie<sup>8</sup> found them in 51 per cent of cases in a similar series. The incidence of node metastases was 30 per cent for the 27 "colloid" cases in our series. In the 10 "colloid" cases of the signet-ring type it was 50 per cent, and in the 17 other "colloid" cases 18 per cent. Rankin and Chumley<sup>16</sup> found node involvement in 58 per cent of all their "colloid" cases.

TABLE XV

INCIDENCE OF LYMPH NODE METASTASES

	<i>Right Colon</i>	<i>Left Colon</i>	<i>Right and Left Colon</i>	<i>Rectum</i>	<i>Colon and Rectum</i>
Total cases	27	78	105	107	212
Cases with node metastases	4	15	19	39	58
Percentage of cases with node metastases	15%	19%	18%	36%	27%

It has already been shown that cases with node metastases usually belong to a more malignant grade. Sixty per cent of cases with node metastases were in Grade III as compared to only 4 per cent in Grade I. A comparison of the follow-up results showed 60 per cent of the cases without metastases, and 23 per cent of those with metastases alive five years without the disease,



making the incidence of survival two and one-half times higher in the former group. The results were based on cases dead from the disease or alive five years with or without it.

**CLASSIFICATION OF TUMORS AS PROJECTING, INTERMEDIATE AND INFILTRATING, FOR PROGNOSIS**—The tendency of a tumor to grow out into the lumen of the bowel or to infiltrate into the surrounding tissues has often been used as a guide to prognosis not only in the large intestine but in other parts of the gastro-intestinal tract. Whipple and Raiford<sup>24</sup> have recently emphasized its use in cancer of the stomach. On the other hand, Dukes<sup>25</sup> believes that such a classification of rectal cancer is misleading, and that these characteristics are simply stages in the life history of the tumor and do not represent different types. He believes that the growth at first projects into the lumen, perhaps arising from a benign adenoma, and that later as it increases in size its projecting portion with a poorer blood supply and greater exposure to infection sloughs away leaving an infiltrating ulcer. It is probable that this sequence sometimes occurs, but that it accounts for the differences in gross pathology in most cases seems doubtful. In our series, the tumors were divided into three groups, projecting, intermediate, and infiltrating. Only cases with gross specimens available for examination were included. The proportion of cases in each group was 29, 49, and 22 per cent, respectively. On comparing the histologic grades of these tumors, the projecting type proved to be mostly Grade I, and the infiltrating Grade III. This is what might be expected, and gives further evidence of the benign character of the projecting tumors as compared with the infiltrating.

The five-year results were far better in the projecting than in the infiltrating cases, as might be expected. This was true both in the colon and rectum. Rankin and Olson<sup>4</sup> reached a similar conclusion from a study of colon carcinomata.

TABLE XVI

## FOLLOW-UP RESULTS IN PROJECTING, INTERMEDIATE AND INFILTRATING TUMORS

		<i>Projecting</i>	<i>Intermediate</i>	<i>Infiltrating</i>
Cases	81	23	42	16
Five-year survivors				
Cases	44	19	19	6
Per cent	54%	83%	45%	38%
Five-year survivors without evidence of disease				
Cases	40	18	19	3
Per cent	49%	78%	45%	19%

This classification is of some value in prognosis. It is similar to that of Dukes but less accurate. The distinction between the three groups is often difficult to make and at best is only approximate.

**REGIONAL VARIATIONS IN GRADE**—Variations in morphology in different parts of the tumor are frequent in cancer of the colon and rectum. For this

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reason, microscopic sections from several areas should always be taken. It is especially important to study the deep infiltrating edge which is often the least differentiated. In about 15 per cent of the cases in this series, such variation made grading difficult. The grade of the more anaplastic of the two areas was usually taken as the grade for the tumor itself. In general, however, the same grade was found throughout the tumor.



FIG 18—Carcinoma of the rectum showing marked variation in morphology and grade in the same tumor (X85)

The relation of the grade of the tumor and that of the metastases in the regional nodes was also studied. All cases were included irrespective of follow-up. There were 62 in all. In 53, or 85 per cent, the grade was the same. In three, or 5 per cent, the grade in the nodes was more malignant than in the parent tumor, and in six cases, or 10 per cent, it was less malignant. That the grade is usually maintained in the metastases, and if changed is as often of a higher as of a lower grade was noted by Gates and Warren,<sup>26</sup> and Mills, Broders, and Caylor<sup>27</sup> in various types of carcinomata, and by Haagen-sen<sup>11</sup> in cancers of the breast.

**COMPARISON OF THE GRADE OF BIOPSIES AND OF THE PARENT TUMOR**—It has long been recognized that biopsies may fail to give a correct picture of the histology of a tumor. The specimen is often too small for adequate

study It only includes one area of the tumor, is usually taken from the surface of the growth, and does not include the deep edge which is often the least differentiated These disadvantages are encountered particularly in judging the invasive tendency of the growth, which has been shown to be one of the most important criteria in grading In 20 consecutive biopsies, Dukes found that the biopsy showed a lower grade than the main tumor in 16 He considered them unsatisfactory for grading On the other hand, Stewart and Spies studied a series of carcinomata of the rectum based entirely on biopsies Although admitting their limitations, they believe that they are adequate for grading and are of definite value in prognosis

In our series there were 74 cases of cancer of the rectum and rectosigmoid in which biopsies were taken and could be compared with sections from the tumor after removal In 58, or 78 per cent of the 74 cases, the biopsy was of the same grade as that of the tumor on later examination In 10 of these cases, the biopsy appeared somewhat less malignant than the tumor, but not enough to receive a different grade In 16 cases, or 22 per cent, the biopsy was at least one grade less malignant than the tumor was rated, and in two cases there was a difference of two grades, the biopsy being Grade I and the tumor Grade III There were no cases in which the biopsy appeared to be more malignant than the tumor itself In addition, it may even fail to give the correct diagnosis A diagnosis of benign adenoma was made from the biopsy in several cases in our series only to be disproved on later examination

*The Size of Lymph Nodes and Metastases*—It is often difficult to determine at operation whether or not the regional nodes are involved The size of the nodes has not proved to be a reliable guide Enlargement is often due to inflammation rather than to metastases In this series, there were 97 cases with nodes reported to be enlarged at operation or in the pathologic examination of the gross specimens Of these, 62 per cent proved to be uninvolved with only 38 per cent showing metastases Of the nodes that showed metastases, only about one-half were reported enlarged In the colon alone the size of the nodes proved even more misleading Only 21 per cent of the nodes reported enlarged were positive

*Annularity*—In over one-half of the cases in the series, or 57 per cent, in which gross specimens were available for study, the growth completely encircled the bowel This was over twice as frequent in the colon as in the rectum, 78 per cent as compared to 34 per cent No special relationship was found between the grade of the tumor and the prevalence of complete annularity The five-year results were considerably better when the tumor was not completely annular than when it was, as might be expected The incidence of five-year survival without disease was 59 per cent in the former group, and 40 per cent in the latter The results did not include the operative deaths, those lost to follow-up, and those dead from other causes

*Age*—Age has long been thought to be an important factor in prognosis Cancer of the colon and rectum in the younger age groups is generally believed to give a poorer outlook Rankin and Comfort<sup>28</sup> found a greater proportion

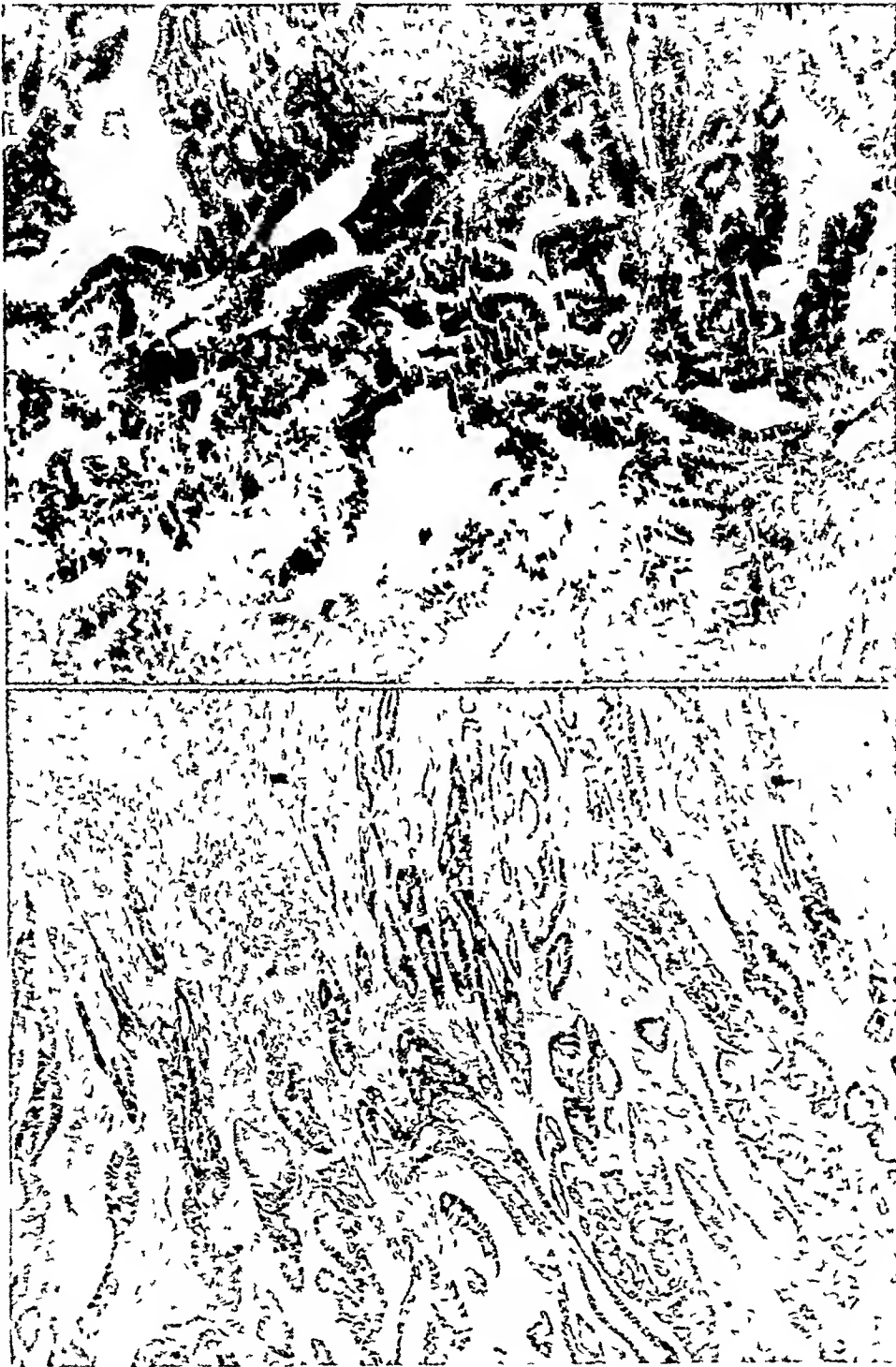


Fig. 19—Carcinoma of the rectum showing biopsy, Grade I on the left and on the right, section from the tumor taken after operation, Grade III (X85)

of higher grade tumors and poorer five-year results in patients age 30 years and less. Shedden<sup>20</sup> also concluded that the grade decreases as the age increases. Stewart and Spies<sup>7</sup> found the average age somewhat less in the most malignant grade in a small series of rectal carcinomata. Gates and Warren,<sup>26</sup> on the other hand, found the relative frequency of the grades to be the same in each age group in a large series of epidermoid cancers. In this series no relationship could be shown between the grade of malignancy and the age of the patient. The results in the different decades were also compared. No definite difference could be demonstrated, however. It is true that between 20 and 29 years of age the five-year survival incidence was only 17 per cent, as compared to a general average of 32 per cent, but there were only six cases in this group.

The average age of both the colon and rectal cases at operation was 52 years. In the right colon cases it was 49 years, slightly less than in the left colon or rectum cases. Most cases occurred in the fifth and sixth decades. The youngest patient was 28, and the oldest 77 years old.

TABLE XVII  
FOLLOW-UP RESULTS IN THE DIFFERENT AGE GROUPS

		20-29	30-39	40-49	50-59	60-69	70-79
Dead of disease or living five years with or without disease	126	4	22	28	40	32	0
Operative deaths	61	2	6	13	21	15	4
Lost to follow-up	18	0	2	3	7	5	1
Dead under five years from other causes	7	0	0	1	1	5	0
Total cases	212	6	30	45	69	57	5
Five-year survivors							
Cases	68	1	12	15	23	17	0
Per cent	32%	17%	40%	33%	33%	30%	—
Five-year survivors without evi- dence of disease							
Cases	61	1	12	13	22	13	0
Per cent	29%	17%	40%	29%	32%	23%	—

**PROGNOSIS BEFORE OPERATION**—The foregoing discussion has been confined chiefly to determining prognosis after operation when complete gross and microscopic specimens are available. Of even greater interest to the surgeon is prognosis before operation. Unfortunately, this is much more difficult. It is only possible to any degree in rectal tumors that can be palpated or seen with the proctoscope and from which biopsies can be obtained. The most important factor in prognosis, the extent of spread of the growth, cannot be accurately determined at this time. The early A cases can perhaps be identified by their mobility, small extent, and tendency to project into the lumen. The more advanced tumors may be suspected by their fixation, greater

degree of annularity, ulceration, and extent Except in certain extreme cases, however, size is not a reliable criterion of operability Moreover, as Westhues<sup>30</sup> has pointed out, fixation to the sacrum or prostate is more often due to inflammatory reaction than to carcinoma Mesenteric node involvement can seldom be determined before operation Westhues has also asserted that there is little relationship between the extent of the growth locally and the presence of liver metastases The histologic grade of the tumor obtained by biopsy is an important aid in prognosis, but indicates only the probabilities of the extent of the growth Biopsy, moreover, is not always reliable and in nearly one-fourth of our cases was one grade less malignant than the true grade of the tumor It should be used with great caution in determining operability in any individual case Thus, even with all the means available, the accurate prognosis of rectal tumors before operation is not yet possible

**FOLLOW-UP RESULTS**—In presenting the results of surgical treatment, the operative deaths, the cases lost to follow-up, and those dying under five years from other causes should be included Otherwise, the results are misleading and present too favorable a prognosis The inclusion of these cases, for example, brought down our five-year results without evidence of disease from 48 to 29 per cent for the colon and rectum Tables XVIII and XIX have been prepared, however, for comparison with other series of cases calculated on similar bases The results in the colon were better than in the rectum, 32 per cent as compared to 25 per cent The right colon showed the best percentage of all, 37 per cent Rankin and Olson also had a somewhat better five-year follow-up in the right colon cases as compared to the left, but could give no explanation for the difference The poorer result in the rectum is in keeping with our previous finding that rectal tumors show a higher propor-

TABLE XVIII

FOLLOW-UP RESULTS

*Operative Deaths, Cases Lost to Follow-Up, and Cases Dead from Other Causes Included*

	<i>Right Colon</i>	<i>Left Colon</i>	<i>Right and Left Colon</i>	<i>Rectum</i>	<i>Colon and Rectum</i>
Cases dead of disease or alive five years with or without disease	14	48	62	64	126
Operative deaths	9	19	28	31	59
Lost to follow-up	2	10	12	6	18
Dead under five years from other causes	2	1	3	6	9
Total cases	27	78	105	107	212
Five-year survivors					
Cases	10	26	36	32	68
Per cent	37%	33%	34%	30%	32%
Five-year survivors without evidence of disease					
Cases	10	24	34	27	61
Per cent	37%	30%	32%	25%	29%

tion of Grade III tumors than the colon and over twice as high a proportion of advanced cases with metastatic nodes, but the difference is less than might be expected. Rankin and Olson had 58, 48, and 51 per cent five-year survivors without evidence of disease in the right colon, left colon, and combined group respectively. Their results show a high incidence of survival but the operative deaths, cases lost to follow-up and dead from other causes were not included.

TABLE XIX  
FOLLOW-UP RESULTS

*Operative Deaths, Cases Lost to Follow Up and Cases Dead from Other Causes Not Included*

	<i>Right Colon</i>	<i>Left Colon</i>	<i>Right and Left Colon</i>	<i>Rectum</i>	<i>Colon and Rectum</i>
Cases dead of disease or alive five years with or without disease	14	48	62	64	126
Five-year survivors					
Cases	10	26	36	32	68
Per cent	71%	54%	58%	50%	54%
Five-year survivors without evidence of disease					
Cases	10	24	34	27	61
Per cent	71%	50%	55%	42%	48%

A comparison of the results with and without node metastases showed, as might be expected, a much better prognosis when the nodes were not involved. Of the combined colon and rectal cases without node metastases, 34 per cent survived five years and were free of disease as compared to 16 per cent of the cases with lymph node metastases. The results were slightly better in the colon than in the rectum when the nodes were not involved, and about the same when they were. The best results were seen in the right colon when the nodes were negative and the poorest when positive. The cases without node metastases represented 73 per cent of all the cases, and those with metastases 27 per cent. This ratio is probably not accurate and should show a higher figure for the cases with involved nodes because of inadequate examination of the lymph nodes in the earlier cases in the series.

Of the 27 "colloid" tumors, seven, or 26 per cent, were alive over five years without disease. This figure is based on all the "colloid" cases and includes operative deaths, cases lost to follow-up, and those dying from other causes. Only one case with involved nodes survived five years. The 17 "colloid" tumors that were not of the signet-ring type showed four, or 24 per cent, living five years without evidence of disease. This result is slightly poorer than the 29 per cent average for the whole series. As most of these "colloid" tumors fell into Grade I, histologically, one would have expected a better result. Of course, the group is entirely too small to warrant a definite conclusion. All cases with involved nodes died with recurrences within five years. Only eight of the 17 cases had follow-ups that permitted analysis.

There were 10 signet-ring tumors in all. Seven had follow-up records suitable for study. There were three five-year survivors without disease, or 30 per cent. Here again the number is too small for any definite conclusions.

Although the five-year results in the two types of colloid tumors have been similar, the higher proportion of Grade III tumors and the much higher incidence of node metastases in the signet-ring cases suggest that they are a particularly malignant group. Parham,<sup>17</sup> Raiford,<sup>9</sup> Rankin and Brodeur,<sup>2</sup> Ochsenhirt,<sup>15</sup> and Rankin and Chumley<sup>16</sup> hold the same view.

#### SUMMARY

(1) A series of 223 cases of carcinoma of the colon and rectum has been studied. Adequate follow-up records were obtained in 205, or 92 per cent.

(2) The following four criteria for histologic grading were found to be of value from our follow-up results: Glandular arrangement, invasiveness, nuclear polarity, and number of mitoses.

(3) Both a numerical and nonnumerical method of grading were tried, based on the four criteria selected. As both gave very similar results, the nonnumerical method was adopted because of greater simplicity. Three grades of malignancy were used instead of the usual four.

(4) Most of the cases were Grades I and II. The percentage of Grade I tumors was 19 per cent higher and that of Grade III tumors 16 per cent lower in the colon than in the rectum, suggesting that colon tumors tend to be better differentiated. Simple "colloid" tumors were mostly Grade I, and those of the signet-ring type nearly all Grade III.

(5) A definite relationship was found between the follow-up results and the grades. The chances of living five years without recurrences were three times as good for the Grade I cases as for the Grade III cases. The same relationship was seen when the cases with and without node metastases were studied separately, although it was less striking. The incidence of metastatic lymph nodes increased with the grade.

(6) The distribution of cases according to Dukes' classification showed a higher proportion of advanced C cases in the rectum than in the colon, with a correspondingly smaller proportion of A cases. Only two out of 69 cases showed node metastases before the bowel wall had been penetrated. Dukes' generalization in this regard has been shown by our series to apply to the colon as well as the rectum.

(7) Follow-up results according to Dukes' classification showed striking differences between the A, B, and C cases. No definitely proven A case died after operation from recurrence. The chance of five-year survival without disease was over four times as good for the A as for the C cases. The value of this classification in prognosis is obvious.

(8) A definite relationship was found between the grades and Dukes' method of classification. Most of the A cases were found, histologically, to be Grade I, and very few Grade III, whereas C cases were mostly Grade III.



and very rarely Grade I. The extent of spread of a tumor at operation is of the greatest importance in prognosis in any particular case, but is in turn based primarily on the rate of growth as evidenced by the grade of the tumor. Both criteria should be used in prognosis to supplement one another. A classification combining both the grade and Dukes' method is presented.

(9) Lymph node metastases occurred in 27 per cent of cases in the whole group and were twice as frequent in the rectum as in the colon. They were present in 30 per cent of the "colloid" cases, occurring in 50 per cent of those of the signet-ring type and in 18 per cent of the other "colloid" cases. The incidence of five-year survival was two and one-half times higher when the nodes were not involved than when they were.

(10) Tumors classed by gross examination as projecting gave far better five-year results than those classed as infiltrating. Most of the projecting tumors were, histologically, Grade I, and the infiltrating Grade III.

(11) Variations in histologic grade in different parts of the same tumor were frequent. The grade of the tumor in the metastatic nodes was usually the same as that found in the main tumor. In 78 per cent of the 76 rectal tumors in which biopsies were taken, the biopsy showed the same grade as the tumor. In 22 per cent of cases, the biopsy was at least one grade less malignant. In no case was it more malignant.

(12) The presence of enlarged lymph nodes is not a reliable indication of metastases. In 97 cases in which the nodes were reported enlarged, only 38 per cent contained metastases.

(13) No relationship could be found between the age of the patients and the five-year results.

(14) The follow-up results which included operative deaths, cases lost to follow-up, and dead from other causes, showed 29 per cent living five years without disease for the combined group, 32 per cent for the colon, and 25 per cent for the rectum.

(15) Of the 17 "colloid" cases not including the signet-ring type, 24 per cent survived five years without evidence of disease, as compared to 30 per cent of the 10 signet-ring cases. Both series, however, are too small to warrant conclusions.

(16) The five-year results without evidence of disease in cases both with and without node metastases showed 34 per cent for the former, and 16 per cent for the latter in the combined colon and rectum group. If the nodes show metastases, the prognosis for five-year survival both in the colon and rectum is just about one-half as good.

#### CONCLUSIONS

The grading of colon and rectal tumors is of definite value for prognosis. It is of less value, however, than the classification of these tumors according to their extent of spread, as outlined by Dukes. A combination of these two methods may prove even more effective.

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# MALIGNANT TUMORS OF THE SALIVARY GLANDS \*

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IN THE earlier reports on tumors of the salivary glands appearing at the end of the eighteenth and the beginning of the nineteenth centuries, no clear distinction was made between those arising in and derived from the salivary glands and other tumors appearing in the regions of the salivary glands but not actually of salivary gland origin. It is probable that certain inflammatory and granulomatous lesions were included. The first attempt at classification seems to have been made by Beiard<sup>1</sup> in his thesis published in 1841. Additional knowledge concerning the character of salivary gland tumors was gained through the works of Lebert,<sup>2</sup> Broca,<sup>3</sup> Richard,<sup>4</sup> and Dolbeau<sup>5</sup> (1850-1858). Their true origin became recognized, and they were described as adenomata or enchondromata. Billroth<sup>6</sup> (1859) and Virchow<sup>7</sup> (1863) made rather detailed gross and microscopic studies and noted their complex structure. Von Bruns<sup>8</sup> (1859) made an histopathologic study of the material from a considerable number of cases and was regarded by Volkmann<sup>9</sup> (1895) as the founder of our knowledge on the subject. Apparently the name "mixed tumors" was established through an article published by Minssen,<sup>10</sup> in 1874, in which they were referred to as "*gemischte Geschwulste*"

During the latter half of the nineteenth century, the origin of salivary gland tumors was a matter of lively interest and difference of opinion. There were three principal schools of thought. One school believed they were derived from connective tissue and, therefore, mesenchymal in origin; Billroth,<sup>6</sup> Virchow<sup>7</sup> and Kaufmann<sup>11</sup> were the chief protagonists of this theory. A second group believed that vascular endothelium constituted the tissue of origin; the names of Kolaczek,<sup>12</sup> Waitmann,<sup>13</sup> Nasse<sup>14</sup> and Volkmann<sup>9</sup> are prominently associated with this group. Volkmann, more than any other, was responsible for the popularization of the endothelial hypothesis. A third group believed that the complex nature of salivary gland tumors could best be explained upon the assumption of branchial origin; Cohnheim,<sup>15</sup> Birch-Hirschfeld,<sup>16</sup> Cuneo and Veau,<sup>17</sup> and Fiedet and Chevassu<sup>18</sup> are closely identified with the earlier development of this thought. A fourth group, largely influenced by the work of Hinsberg,<sup>19</sup> believed that detached or displaced embryonal salivary gland cells were responsible for the later formation of tumors. A fifth group, largely of the French school, attributed the development of salivary gland tumors to a simple direct origin from glandular

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epithelium, Verneuil,<sup>20</sup> Planteau<sup>21</sup> and Duplay<sup>22</sup> were supporters of this point of view

It cannot be said that any wholly satisfactory hypothesis has been developed. Difficulty has been encountered in offering a suitable explanation for the frequent occurrence together of epithelial, cartilaginous, myxomatous and fibrous tissues in a single tumor. The majority of investigators subscribe to the theory of epithelial origin, but there is some difference of opinion as to the actual mode of development. Pitancé,<sup>23</sup> in 1897, suggested that the parenchymal cells of mixed tumors were derived from masses of cells left in or about the gland during the process of development. Hinsberg<sup>19</sup> did a large amount of embryologic research, the results of which supported the epithelial origin of salivary gland tumors and indicated that they arise from embryonal glandular elements. Wilms<sup>24</sup> and Wood,<sup>25</sup> however, have placed the time of detachment of epithelial cells to a still earlier period of embryonic development. According to their belief the detachment occurs before the salivary glands are formed. It is not, therefore, embryonic parotid tissue which becomes disorganized but rather a displacement of the buccal epiblast from which the parotid is subsequently to be formed. Some underlying mesoblast is assumed to be included in the ectopic process. By the assumption of an early displacement it is easier to explain the presence of epithelial cells with intercellular bridges or spines which have frequently been observed in salivary gland tumors. The close association of cartilage, myxomatous tissue and other structures of mesoblastic origin also becomes more comprehensible.

To further clarify the probable manner of growth of salivary gland tumors, it appears worth while to review in some detail the embryonic development of a normal gland. According to Hammar<sup>26</sup> the beginning of parotid development is seen by the end of the first month, the embryo then being about 8 Mm long. A groove appears in the sulcus of the cheek near the angle of the mouth. Grosser<sup>27</sup> and his associates describe the further development as follows: "At first quite small, the furrow gradually elongates, and before the embryo has reached a length of 17 Mm it separates from the epithelium and forms a tubular structure lying beneath the epithelium of the alveolobuccal groove and opening into the mouth cavity at a point which corresponds with the anterior end of the original furrow. Mesenchymatous tissue gradually forces its way between the tube and the alveolobuccal epithelium, and the tube, increasing in length, pushes its way back over the masseter muscle to the neighborhood of the external ear. As it comes into this region the tube or duct, as it may be called, begins to branch at its posterior extremity, the branches being at first solid outgrowths from the wall of the duct, and, as these increase in number and size and become surrounded by a mesenchymatous capsule, the gland assumes the position and general form of the adult structure. The histogenetic development of the salivary glands is not completed until some time after birth, probably not until after the child is weaned. The canalization of the solid anlagen of the glands proceeds peripherally, and so long as the terminal branches remain solid they have

the power of producing additional buds. When, however, the lumen is formed in a bud and it becomes an alveolus, its power of budding is lost, and the further increase in the size of the gland is due to the development of the investing connective tissue and to an increase in the size of the alveoli already present."

Our special attention is drawn to the apparent capacity of the solid anlagen of glands to continue to grow and produce buds until canalization takes place. If groups of cells became detached from the embryonic gland or from buccal epiblast and were subsequently activated, it is quite conceivable that their development might follow a course of the fetal type. Faulty canalization or failure of canalization would be followed by continued epithelial budding and growth. With the concomitant development of an investing connective tissue capsule, a tumor would be formed. If growth were orderly and development of the capsule kept pace with the epithelial elements, such a tumor should remain encapsulated and benign. If, on the contrary, the rate of epithelial proliferation became excessive, there would be invasion of adjacent tissues, and the tumor would be called malignant.

Salivary gland tumors, if derived from primitive embryonal tissues, may reasonably be expected to show considerable diversity of structure and this indeed is the case. A number of types are found in both the benign and malignant groups. The common types of malignant tumors are (1) The mixed tumors with malignant changes, (2) tumors composed of small cells of the basal type either with solid or cylindromatous arrangement, (3) papillary cystic tumors, (4) adenocarcinomata, (5) squamous cell carcinomata, and (6) a somewhat heterogeneous group, usually rather undifferentiated, and not conforming to any of the preceding classifications.

The tumors behave, clinically, somewhat as their cellular structures would indicate. Metastatic lesions generally follow the pattern of the original tumor. In the case of the malignant mixed tumors the secondary implants usually appear in simpler form. Occasionally, however, the metastatic tumors greatly resemble ordinary mixed tumors, even to the extent of being circumscribed or encapsulated. Such cases have been reported by Tommasi,<sup>28</sup> Griffin and Trombetta,<sup>29</sup> Barozzi and Lesne,<sup>30</sup> Le Dentu,<sup>31</sup> Partsch,<sup>32</sup> Kornblith<sup>33</sup> and McFarland.<sup>34</sup>

When metastasis occurs, the regional lymph nodes are occasionally involved but not with great frequency. In 27 cases from the records of St. Luke's and New York Hospitals (Tables I and II) lymph node involvement was proved in only four, approximately 15 per cent. Metastasis to the lungs was demonstrated roentgenologically in eight of the 11 cases which were examined, an incidence of approximately 30 per cent for the entire series. In 16 patients no roentgenologic examinations of the chest were made. It is quite possible that a more complete study of this group would have added to the incidence of pulmonary metastasis. Bones were involved in two cases. General metastasis occurred in one case. In 82 cases of definite malignancy of the large salivary glands, reported from the Radiumhemmet by

Ahlbom,<sup>35</sup> metastases were reported in the lymph nodes in nine instances (11 per cent), seven to lungs (85 per cent), seven to bones, and five cases with general metastasis. In 42 cases, reported by Stein and Geschickter,<sup>36</sup> there was enlargement of the cervical lymph nodes in 13, or 30.9 per cent. Actual metastasis, however, was proved in only one case. Metastasis to the lungs apparently was not observed in any case. Mediastinal metastasis was recorded in one case. The authors state that distant metastases are extremely rare.

The development of metastatic lesions does not appear to bear a close relationship to the duration of the disease. One patient (Table I, No. 121-135) had histologically proven metastasis to a cervical node and roentgenologic evidence of pulmonary metastasis, both in less than two years after the



FIG 1—Case 59045, Table I. Roentgenogram of chest, 21 years after appearance of original parotid tumor, showing pulmonary metastases. It is probable that the tumor was primarily benign and that malignancy was a later development. The patient lived two years and four months after this roentgenogram was taken and had very few subjective symptoms.

FIG 2—Case 93866, Table I. Roentgenogram taken 20 years after appearance of a submaxillary tumor showing extensive pulmonary involvement. The primary tumor had been excised 19 years before and histologically diagnosed as a "mixed tumor."

apparent onset of the primary tumor. Another patient (Table I, No. 293-784) showed no roentgenologic evidence of pulmonary involvement nine years after onset, but the following year unmistakable shadows were present. Additional examples of delayed metastasis are to be seen in Figures 1 and 2.

The tendency of malignant salivary gland tumors toward remote metastasis, with relatively infrequent involvement of the regional lymph nodes, is in marked contrast with the behavior of other malignant epithelial tumors arising in the same general vicinity. Carcinoma of the tongue and buccal mucosa, for example, regularly metastasizes to the cervical lymph nodes and rarely extends beyond them. Billroth<sup>6</sup> was impressed by the relative infrequency of regional lymph node involvement in carcinoma of the salivary glands, and concluded that these tumors rarely gave rise to metastasis.

Tumors of the salivary glands, as recorded from a number of clinics, have shown considerable difference in the incidence of malignancy. Wood<sup>25</sup> placed

it at 25 per cent of the face and neck group Nasse<sup>37</sup> found two carcinomata and two sarcomata in 36 cases, 11 per cent Volkmann<sup>9</sup> reported one carcinoma and one fibrosarcoma in 33 cases, 6 per cent In the group of cases from the Massachusetts General Hospital, Benedict and Meigs<sup>38</sup> recorded 41 benign tumors, 21 carcinomata, and nine sarcomata, an incidence of malignancy amounting to 42 per cent In the series of parotid tumors reported by Stein and Geschickter,<sup>36</sup> there were 42 malignant tumors in a total of 241 cases, 17.4 per cent Ahlbom<sup>35</sup> reported 82 cases of definite malignancy in 193



FIG. 3.—Carcinoma of the parotid occurring at the age of 29. The rather smooth contour and gentle slope of the tumor indicate its infiltrating character. Benign lesions are frequently irregular and often stand out in a more striking manner.

tumors of the large salivary glands, 42 per cent In 150 consecutive cases from the records of St. Luke's Hospital, New York, Shore<sup>39</sup> found malignant tumors making up 11 per cent of the total Among the entire population, however, malignancy is relatively infrequent The 82 cases reported by Ahlbom constitute the largest series thus far assembled

The symptoms are few and by no means pathognomonic A small nodule or swelling appears without apparent cause and increases in size, usually slowly, but sometimes rapidly There may be a history of the previous removal of a tumor from the same gland When a tumor recurs after being removed completely and without rupture of its capsule, malignancy should be suspected even if the original tumor was histologically benign As a rule there is no pain, when present, it is usually described as shooting or stabbing in character and is referred to the jaw, side of head, or ear A large growth sometimes interferes with motion of the jaw, attempts to open the mouth

widely may cause pain by compressing the tumor. In advanced cases there is frequently a spontaneous facial paralysis due to nerve involvement.

In appearance, the malignant tumor cannot be accurately distinguished from one which is benign. Frequently the malignant lesion appears as a rather even elevation with margins which are not well defined (Fig. 3), whereas, the benign tumor often presents as a precipitous, nodular swelling. On palpation the malignant tumor is usually quite hard and fixed to the deeper structures. Less frequently there is fixation to the skin as well. In late cases there may be ulceration or a facial paralysis. The limits of the tumor as a rule are not easily defined. The palpation of more than one tumor mass is strongly suggestive of malignancy. A benign tumor is ordinarily a well encapsulated, freely movable, firm, resilient, often lobulated, single tumor.

Other conditions which may be confused with tumors of the salivary glands are those affecting the groups of lymph nodes which are intimately associated with glands. Branchiogenic tumors and cysts, tumors of the jaws, and inflammatory conditions are also mistaken, now and then, for new growths of salivary gland origin.

Histologic differentiation of benign and malignant salivary gland tumors is sometimes extremely difficult. A malignant tumor may appear encapsulated and be indistinguishable microscopically from a benign growth. The diagnosis in such cases depends ultimately upon the clinical course of the disease. In the average case the histologic diagnosis is made with relative certainty.

Treatment of the malignant tumors is far from satisfactory. Radical surgery frequently carries the handicap of producing facial nerve paralysis when applied to parotid tumors, and these constitute the great majority. In many cases it also fails to completely eradicate the tumor. Radiation has the disadvantage of threatening the integrity of normal tissues, especially the skin, if given in dosage sufficient to destroy the tumor. A combination of surgery and radiation appears to have given better results than either used alone and has been adopted as the standard treatment in a number of clinics. There is, however, considerable variance in the experiences and views expressed in the literature. Wakeley,<sup>40</sup> Benedict and Meigs,<sup>38</sup> and McFarland<sup>34</sup> saw little benefit from radiation, whereas, Quick and Johnson<sup>41</sup> apparently regarded it as the treatment of choice. Bérid,<sup>42</sup> Wickham,<sup>43</sup> Causse,<sup>44</sup> Hintze,<sup>45</sup> Ahlbom<sup>35</sup> and, in fact, most clinicians of to-day favor a combination of the two agencies.

The application of both surgery and radiation in the treatment of a particular case naturally raises the question as to which is chiefly responsible for the result obtained. A conclusive answer to this question has not been reached and must await further experience. The quality of surgery or radiation employed and the type of tumor are, no doubt, matters of importance. Surgery which does not completely remove the tumor cannot be expected to effect a cure, the same is true of radiation which fails to destroy



all of the tumor cells. To a restricted degree, each method can supplement the work of the other, but it is also true that there is an overlapping of their limitations, particularly in the case of advanced lesions.

The complications associated with surgical extirpation are those incident to any other operation of like magnitude about the face and neck. There are, in addition, the injuries to the facial nerve which are frequently made necessary by inclusion of the nerve in the tumor mass. When a complete division has been produced, it is sometimes possible to restore continuity by suture of the nerve ends. If the ends are separated by a considerable distance, the nerve grafting procedure described by Duel<sup>46</sup> may be tried. Another procedure is the grafting of the spinal accessory<sup>47</sup> or the hypoglossal<sup>48</sup> nerve to the distal segment of the facial. If it is impossible to restore innervation, fascial transplants<sup>49</sup> or muscular rearrangements<sup>50</sup> may be made in order to ameliorate the condition.

The principal complications of radiotherapy are the occasional radiation necrosis, atrophic changes in the skin and deeper tissues with postirradiation dermatitis or ulcer, and atrophy of the salivary and mucous glands with consequent dryness of the mouth. Heavy radiation is also sometimes followed by facial paralysis.

Prognosis in the individual case is a matter of great uncertainty. If untreated, the disease progresses at a rate which cannot be predicted. In some cases it runs a very slow course over many years, in others the progression is rapid and death may occur within a year of the apparent onset. Death may come through gradual exhaustion, from ulceration with infection or hemorrhage, from pulmonary or other metastasis, or from intercurrent disease.

In the treated cases a certain rather low salvage is obtained. Surgery alone gave 20 per cent of three-year remissions and 13 per cent of five-year remissions in the 42 cases reported by Stein and Geschickter.<sup>36</sup> Hintze<sup>45</sup> reported a five-year remission in 26 per cent of a series treated mainly by surgery with some postoperative radiation. Benedict and Meigs<sup>38</sup> could report out of 30 malignant tumors of the parotid only one living and well three years after treatment. All were treated by surgery, with or without radium.

In 62 cases of malignant salivary and mucous gland tumors treated by radiation alone, Ahlbom<sup>35</sup> reported that 39 had been followed for five years and that nine, or 23 per cent, were free of signs and symptoms. Of 55 cases followed three years, 15, or 27 per cent, were well.

Ahlbom reported, in the same article, 62 similar cases treated by surgery and radiation combined. Thirty-five had been followed five years and 14, or 40 per cent, were free of disease. Fifty-five had been followed three years, and 27 of these, or 49 per cent, were well. In 82 cases of definitely malignant tumors of the large salivary glands analyzed in Ahlbom's series, there were 12, or 14.3 per cent, who survived five years or more without recurrence. There were six others, 7 per cent, free of recurrence for more than three but less than five years. One of the five-year survivors was treated by radiation alone, all the others had surgery and radiation. Berard<sup>51</sup> and his asso-

ciates have reported 15 cases of histologically verified cancer of the parotid treated by a combination of surgery and radiation with five, or 33 per cent, well after three years and three, or 20 per cent, well after five years

In 27 cases of carcinoma of the large salivary glands taken from the records of St Luke's and New York Hospitals (Table I), all except two had one or more attempts at surgical extirpation. None had preoperative radiation. Fourteen had postoperative radiation. Two were treated by roentgenotherapy alone, after a preliminary biopsy.

Out of the group of 27 patients, only three, approximately 11 per cent, are known to have been living and well more than five years after operation. One of these, with a parotid carcinoma, had a single operation with no radiation and is now well ten years after operation. Another patient with parotid carcinoma had two operations with postoperative radiation and is known to have been well seven years after the second operation. A patient with a submaxillary salivary gland carcinoma had a single operation with no radiation and is now living and well nine years after operation. One patient, Dr M. K. Smith's case with a sublingual salivary gland carcinoma, is living 17 years since the appearance of the tumor and nine years since the last operation, but has local recurrence and metastasis to the lungs. Operation in this case was followed by roentgenotherapy.

In addition to the survivals of more than five years, there are some of shorter duration. One patient, who had a parotid carcinoma, is well two years and seven months after operation, and another who had submaxillary carcinoma is well two years and six months after operation. There are seven additional patients who are apparently free of disease, but all for a period of less than two years. It is possible that the continued survival of some of this group will increase the number of five-year remissions.

As a rule, carcinomata of the large salivary glands are visible, palpable, accessible tumors, characterized by slow growth and late metastasis. According to the usual criteria, such tumors should lend themselves readily to treatment and offer a good prognosis. It is obvious, however, that such has not been the case. The intimate association of parotid tumors with the facial nerve unquestionably accounts for many failures, particularly in surgical treatment. Patients are frequently advised to ignore tumors in the parotid gland because there is danger of injury to the nerve. Facial paralysis is a serious handicap and neither patient nor physician can be blamed for wishing to avoid it. It is to be remembered, however, that from 10 to 40 per cent of the large salivary gland tumors are either primarily malignant or become malignant. If such a tumor is permitted to grow, the time inevitably comes when it must be removed under conditions which make nerve destruction almost a certainty. It is undoubtedly better to advise removal of all salivary gland tumors when they first come under observation. In the case of a benign tumor serious damage to the facial nerve is seldom necessary. If the tumor is malignant, early removal offers the best chance of avoiding nerve injury and of cure.

TABLE I  
MALIGNANT TUMORS OF THE SALIVARY GLANDS  
*Records of St Luke's and New York Hospitals*

PAROTID GLAND

History No	Sex	Age	Duration of Tumor Before First Treatment	IRRESISTANT		Histologic Diagnosis	METASTASIS			LIVING		DEVELOPMENT OF RECURRENCE	
				Number of Operations	Radiation Preoperative Postoperative		Cervical Nodes	Lungs	Bones	General	Since Appearance of Tumor	Since First Operation	After First Appearance of Tumor
14-026	M	54	4 yrs	1	—	Carcinoma	—	—	—	1 1/2 yrs 6 mos	6 mos	—	—
121-681	F	67	1 yr	1	0	Squamous cell carcinoma	—	—	—	2 yrs	1 yr	—	—
121-135	M	51	8 mos	2	0	Carcinoma	+	—	—	1 yr 9 mos	6 mos	—	—
101-777	F	29	3 mos	3	0	(1) Pap cystoid (2) Adenocarcinoma	—	—	—	1 1/2 yrs 7 mos + 2 1/2 yrs 7 mos	—	—	—
01903	F	52	1 yr	16	—	Carcinoma	—	+	+	—	—	11 yrs	10 yrs
88910	M	15	1 yr	6	—	Adenocarcinoma	—	—	+	—	—	6 1/2 yrs	5 1/2 yrs
35895	F	56	6 mos	1	—	Carcinoma, pap type	—	+	—	—	—	2 yrs	1 1/2 yrs
75813	M	10	9 mos	1	0	Squamous carcinoma	—	—	—	—	—	—	12 mos
75735	F	10	—	1 (biopsy)	—	Squamous carcinoma	—	—	—	—	—	—	—
66353	M	36	5 yrs	3	—	Carcinoma	—	—	—	—	—	—	—
66661	F	17	2 yrs	1	—	Epithelioma	—	—	—	—	—	—	—
59015	M	55	17 yrs	7	0	(1) Mixed tumor (2) Carcinoma	0	+	0	12 yrs	10 1/2 yrs	22 yrs	5 yrs
1211	M	64	—	1	—	Carcinoma	—	—	—	—	—	—	—
17	M	34	—	5	—	Carcinoma	+	—	—	—	—	—	13 yrs
195-872	M	53	2 yrs	2	0	Squamous and adenocarcinoma	+	0	0	6 yrs	2 mos	—	—
203-781	F	20	2 yrs	1	0	(1) Adenocarcinoma (2) Mixed tumor	—	+	0	10 yrs	1 mos *	—	—
101-732	M	11	—	1	—	Malignant mixed tumor	—	—	—	—	1 yr 7 mos	—	—
205751	F	17	3 yrs	1 (biopsy)	—	Carcinoma	—	+	—	—	—	1 yr	—
201119	F	16	3 yrs	2	—	Adenocarcinoma	—	—	—	—	—	—	—
205911	M	58	7 mos	1	0	Carcinoma	+	—	—	—	—	—	—
236160	F	10	8 yrs	1	—	Basal cell carcinoma	—	—	—	—	—	11 yrs	3 yrs
288965	M	10	2 1/2 yrs	1	—	Adenocarcinoma	—	—	—	—	—	1 1/2 mos	—

SUBMANDIBULAR GLAND

95866	F	11	6 mos	1	0	+	—	—	—	—	—	—	20 yrs 6 mos	20 yrs
73181	M	57	6 mos	1	0	(z) Mixed tumor	—	—	—	—	—	—	—	—
138-278	F	64	2 yrs	1	0	(x) Carcinoma, cylindroma type	—	—	—	—	9 yrs 6 mos	0 yrs	—	—
118-101	M	67	5 mos	1	0	Carcinoma	—	0	—	—	3 yrs 5 mos	1 yr 5 mos	—	—
						Idiopathic carcinoma	—	0	—	—	—	—	0 mos	6 mos

SUBLINGUAL GLAND

91108	F	31	3 yrs	8	0	+	—	—	—	—	17 yrs +	9 yrs	—	—
						(z) Mixed tumor	—	—	—	—	—	—	—	—
						(x) Adenocarcinoma	—	—	—	—	—	—	—	—

\* Living, with metastases

+ Living, with recurrence and metastases

SUMMARY

Malignant tumors of the salivary glands in the great majority of cases are epithelial in origin and are classified as carcinomata

They probably arise in displaced embryonal cells of the salivary glands or more likely from the buccal epiblast with some underlying mesoblast

They exhibit a wide variety of histologic structure and of clinical behavior

They affect the sexes in nearly equal numbers and may occur at almost any age The youngest of the present series was 16 years old, the oldest 68 years, the majority appeared in middle life

Some apparently arise as malignant tumors while others appear to be the result of malignant changes in primarily benign tumors

The disease may run a fatal course within a few months or the patient may survive for many years with the disease

Metastasis to the regional lymph nodes is relatively infrequent The incidence was approximately 15 per cent in the present series of 27 cases

Metastasis to the lungs is perhaps more common than is generally recognized Eleven patients of this series had roentgenologic examinations of the chest Eight showed convincing evidence of pulmonary metastasis, an incidence of 72 per cent of those examined and approximately 30 per cent of the entire series A roentgenogram of the chest should be a routine procedure in the study of these cases

The treatment which appears to have given the best results is surgical extirpation combined with radiotherapy

The result in a given case cannot be predicted with any great accuracy The general prognosis can scarcely anticipate the ultimate cure, or five-year survival, of more than 25 per cent

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DISCUSSION—DR N CHANDLER FOOT (NEW YORK) The origin of tumors of the salivary glands is still far from being settled. A good many authorities are inclined to the fetal rest theories, rather than that of parotid origin. The theory of their origin from portions of the buccal epiblast is particularly alluring. Their origin from the parotid itself would scarcely explain the very pleomorphic structure of these tumors. On the other hand, unmixed tumors do occur in the parotid and these are quite uniform structures. This may mean that some of the group do indeed arise from salivary gland, but it might also indicate that only one element of the buccal epiblast has expressed itself in the tumor. It may be, too, that there are more than one source of origin for these tumors. This, however, would seem to be rather far-fetched.

Doctor MacFee has spoken of tumor growth outstripping capsular growth and thus breaking out into the surrounding tissue to become malignant. This breaking through the capsule is a good starting point for formulating tumor malignancy in these cases as, unfortunately, one can tell very little histologically. To many tumors that Doctor Foot has seen, he would unhesitatingly have given a clean bill of health, had he known nothing of the surgical history of the case. On the other hand, outspokenly malignant-looking examples may be well encapsulated and often bring contumely upon the pathologist who views them with alarm and gives a gloomy prognosis. Doctor Foot had had a patient with a completely innocent-looking tumor return on three occasions to the hospital, the last time with apparent pulmonary metastases. This tumor was very poorly, if at all, encapsulated, and invaded the muscle in the parotid region. For these reasons, Doctor Foot felt it of the utmost importance that the pathologist should be acquainted with the surgical data concerning a mixed tumor of the parotid, before attempting to give a prognosis.

The large tumor of unmixed nature, that Doctor MacFee removed from the parotid region, was grossly opaque, light yellow and very firm, so that it resembled parotid tissue somewhat. Under the microscope, however, it seemed to be made up of cords of cuboidal cells with a delicate stroma filled with capillaries, separating the cords and resembling the structure of a paraganglioma and hence carotid body. Doctor Foot could not quite make up his mind whether this was a carotid body tumor displaced slightly higher than usual, or a rather atypical offspring of the parotid which had failed to take on mixed characteristics.

DR ROBERT H KENNEDY (NEW YORK) called attention to one very black side of the tumors under discussion worth emphasizing, at least as they present themselves at the Skin and Cancer Hospital. Almost invariably, when operation is performed upon them there, it is anywhere from the second to to the tenth or twelfth time. The impression is gained there that most of these tumors originally were operated upon by a surgeon or a general practitioner who took them as a rather simple procedure, operating most commonly under local anesthesia, believing that the tumor, which is apparently possibly 1 cm or 1.5 cm in diameter, represents the entire growth, when as a matter

of fact it really represents the prominence of the parotid fascia over a tumor that has not yet broken through, or if it has broken through, the fascia does not disclose the deep part at all. In view of the statistics presented by Doctor MacFee regarding chance of recovery, and the fact that the pathologist cannot tell in many cases which are the malignant tumors and which are not, the small tumors that one sees in the parotid region deserve particular preparation for very thorough operation the first time one sees them. Doctor Kennedy said he felt that the procedure he had learned from Doctor Semken was the best one to carry out for these tumors, namely, a crucial incision for a parotid tumor of any size at all, then dissecting up the four quadrants and suturing them back. The dissection is made as much as possible from above downward so that one runs in the direction of the facial nerve. If there is any possibility that that nerve runs through the tumor, it is, of course, most essential to attempt to save it. Occasionally one finds that the tumor is in the superficial portion of the parotid and has so compressed the major portion of the gland that the facial nerve is well pressed away from the tumor, still lying in the parotid tissue.

Doctor Kennedy felt that it was inexcusable to use radiotherapy in preference to operation, as is still practiced in a good many cases. He had never seen it do anything except possibly cause recession for a time, and in numerous cases where a biopsy was performed with a diagnosis of benign tumor, after multiple radiation treatments, the patient comes in with a very malignant growth.

DR HUGH AUCHINCLOSS (NEW YORK) said that of recent years the seriousness of the prognosis in these cases had come to be more fully appreciated. It seems plausible, owing to the frequency of lung metastases in these cases, to perform a preliminary ligation of the external and internal jugular veins, if an attempt at removal be made. It is more than likely that these tumors have their distribution by means of the blood stream.

Doctor Auchincloss described a patient, a middle aged woman, who was sent to him within the last year in consultation from a neighboring state. A small specimen had been removed from the right parotid region previously. The left parotid was swollen and strongly suggested new growth. He removed a specimen from the left side and Doctor Stout made the diagnosis of a reticulocytoma. A Wassermann reaction was not done at that time, but shortly afterwards it was done and found to be double 4 plus. It is probable that she had congenital syphilis. In spite of this, Doctor Stout thinks that the Wassermann reaction had nothing to do with it, and it is more than likely that he was right. In all events, both sides have been treated by roentgenotherapy, with a resultant very rapid subsidence. One cannot be at all sure, however, that this has cured her. It is not unlikely that it may appear elsewhere. She has also been given antisyphilitic treatment.

Another small tumor, that Doctor Auchincloss stated he had seen, was in a woman of middle age. It was removed and found to be a so-called "mixed, or composite tumor." Within two years it recurred. It was again removed, and treatment by radium inaugurated, which resulted in a very definite subsidence of the growth. Two years later, she was submitted to very heavy radiation at Johns Hopkins Hospital because of the diffuse persistence of the disease, with facial paralysis. Three weeks ago she died.

As brought out so ably by Doctor MacFee, these tumors should be regarded with great concern. Doctor Auchincloss said he had records of a few other cases that have remained well, in younger people.



DR JOHN M HANFORD (NEW YORK) said that the record of Dr A P Stout, estimated for a ten-year period (1915-1924), at the Presbyterian Hospital, indicates that in that period there were only three carcinomata of the parotid gland—of all the salivary glands in fact—in a total of 1,862 cases of carcinoma. It is a rare condition. He asked Doctor MacFee what his procedure is when he operates upon a supposed composite tumor (Doctor Hanford felt sure that carcinomata are not usually diagnosed beforehand, especially the small ones) and concludes, or suspects, during the operation that it is carcinoma.

Doctor Hanford disagreed somewhat with both Doctor Foot and Doctor MacFee in their discussion of the encapsulation of composite tumors. His impression was that they really do not have capsules—that is, neither the carcinoma nor even the mixed or composite tumor. They are circumscribed and appear to have capsules in the sense that a fibroma has a capsule, but he believed that even the composite tumor has not a real capsule. He would also disagree with Doctor MacFee, though having learned a great deal from him, that the most common thought one should have, when a composite tumor has been operated upon and recurrence appears, is that the reappearance is indicative of malignancy. The reappearance of these tumors after attempted excision is very common. The fact is that occasionally even after enucleation of what appears to be a capsule, there are still some composite tumor cells left in the parotid gland.

DR MORRIS K SMITH (NEW YORK) said that in his case—tumor of the sublingual gland—the tumor palpated in the floor of the mouth was about the size of a peanut, and it was excised through an incision in the floor of the mouth. The first recurrence was treated similarly. He said, however, that although he probably would not have the chance to operate upon another sublingual mixed tumor, he would—if he did have such an opportunity and were sure of the diagnosis—make an approach, even though it involved undertaking a considerably more extensive procedure, which insured a wide removal without any risk, if possible, of leaving behind a portion of it. In operating in as small a field as the floor of the mouth it is technically extremely easy not to accomplish a complete enucleation, particularly if the capsule is very thin and there are cysts.

DR HERBERT WILLY MEYER (NEW YORK) emphasized that cancer of the parotid gland is of vital import to the patient as well as to the surgeon, if a radical operation is indicated with the resulting injury to the facial nerve, particularly in the female.

From a survey of the records of the past ten years at the Lenox Hill Hospital, made by Dr Richard Kessler, Doctor Meyer noted nine cases of malignancy of the parotid salivary gland. The youngest case was in a child, age 4, who had a sarcoma of the parotid, proven by biopsy, which was treated by deep roentgenotherapy, held partially in check, and then died 14 months later of a brain metastasis. The oldest case was in a man, age 68, who had a radical, complete extirpation of the parotid gland and is alive to-day, ten years later.

In four of the cases, a small tumor had been noted for a number of years which then suddenly began to increase in size. In three cases, a preoperative diagnosis of malignancy was made, in the remaining six, a cyst or mixed tumor was diagnosed. One of these, a boy, age 14, was operated upon with a diagnosis of sebaceous cyst, but at operation it was found to be an encapsulated tumor within the parotid gland. Pathologic diagnosis was a squamous cell carcinoma arising in a mixed tumor. This patient is now clinically well, eight years after operation.

Two of the nine cases were not operated upon, as the condition was so far advanced that operation was impossible. Biopsies were taken in these cases and diagnosis confirmed pathologically. One of these was the child with sarcoma of the parotid, previously referred to. The other was a patient, age 65, who had a number of roentgen ray treatments, and was then lost track of, probably having died.

Of the remaining seven cases, the tumor was removed primarily in each instance. Two of these cases were lost track of, one died following operation, in whom the tumor had extensively invaded the surrounding tissues. One patient died eight years after the primary excision of the tumor from the parotid gland. This patient had local recurrences involving bone and surrounding tissues. Irradiation did not hold this in check and the patient finally died. Roentgenologic examination of his chest shortly before death did not reveal pulmonary metastases such as Doctor MacFee has shown. As a matter of fact, chest roentgenograms were taken in only two of our nine cases, and both of these were negative.

The remaining three cases operated upon are alive and well, one ten, another eight years after operation, and the third, a recent case. One of these was a man, age 68, who had noticed a mass in the region of the right parotid gland of six months' duration. There were a number of masses, which impressed one as being lymph-nodes, either tuberculous or malignant. On April 5, 1928, the main tumor mass was removed from the gland, and included the lower pole of the parotid which contained the smaller nodules. Pathologic diagnosis showed these masses to be diffuse adenocarcinoma of the parotid. Three weeks later, therefore, under colonic ether-oil anesthesia, the entire parotid gland, with overlying skin surrounding the previous scar, was removed with a block dissection of the cervical lymph nodes, including the submental, submaxillary, omohyoid, carotid, posterior digastric and posterior deep chain groups of nodes. These nodes were removed in one mass with the parotid gland, and a pedicle flap from the posterior portion of the neck was made use of to close the defect in front of the ear. Pathologic diagnosis showed extensive areas of tumor, deep within the parotid and infiltrating the previous operative scar. No lymph nodes were found to be involved. On February 7, 1929, a strip of fascia lata was placed under the eye, from the inner canthus high up onto the parietal portion of the scalp. On December 16, 1931, a strip of fascia data was placed from the zygomatic arch to the angle of the mouth, hooked around the orbicularis oris muscle and brought back to the zygomatic arch. These two fascia lata strips have helped quite materially in overcoming the effects of the facial paralysis, and at least have formed a sling which partially prevents the flapping of the flaccid cheek when the patient talks. Some authors have made use of strips of temporal muscle turned down and fastened to the angle of the eye and angle of the mouth to overcome the paralysis. This patient has remained clinically well for ten years and is now 78 years of age.

In a recent unusual case of papilloma arising from a duct within a cyst of the parotid gland, Doctor James Ewing expressed himself that irradiation was apparently not the method of choice in the treatment of carcinoma of the parotid gland.

According to our small group of cases, it seems that carcinoma arising in a mixed tumor seems to stay well with local excision, while diffuse adenocarcinoma arising from the ducts of the gland is apparently best handled by radical extirpation of the entire gland with the accompanying lymph nodes.

DR WILLIAM F MACFEE (concluding) said, in regard to ligation of the jugular veins, that it had not been done in any of the cases he reviewed. It is a suggestion which might be taken into consideration because of the frequent metastases to the lungs, a danger which has not been generally appreciated. He said he certainly had not suspected that anything like 30 per cent of the cases of salivary gland carcinoma would ultimately develop lung metastases. When it is realized that only 11 cases had roentgenograms of the chest, and that eight of these showed metastases, the probability is that an even greater number of the series had thoracic involvement.

Regarding the procedure, when a benign tumor has been anticipated but malignancy is discovered, Doctor MacFee said that if complete removal would involve destruction of the facial nerve, and he had not obtained consent of the patient beforehand, he would desist for the time being. It is frequently impossible to determine the character of a tumor before operating. In response to Doctor Hanford, Doctor MacFee said that, whereas, these tumors may not be encapsulated in the pure sense of the word, many of them do have a fibrous covering which is described by the pathologist as a capsule and which to most of us is indistinguishable from a capsule.

One hint with regard to malignancy. Inclusion of the facial nerve in a tumor is a strong point in favor of malignancy. It is unusual for a benign tumor to actually incorporate the nerve. The parotid gland itself develops, primarily, external to the facial nerve, the vast majority of benign tumors are likewise external to the nerve and tend to push it aside as they develop. Malignant tumors, on the other hand, may actually include it.

Concerning recurrence after complete removal. If a tumor first comes under observation as a recurrence, there is frequently no way of knowing exactly what was done at the original operation. Sometimes, however, there is recurrence at the site of a tumor which is known or believed to have been completely removed. In such a case the possibility of malignancy should be seriously considered.

# MIXED TUMORS OF THE SUBLINGUAL GLAND\*

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MIXED tumors of the sublingual gland, strangely enough, considering their frequency in the parotid, are very rare Dr B R Shore<sup>1</sup> informs me that, in the files of the Pathologic Department of St Luke's Hospital, during the past 40 years, there are recorded 135 mixed tumors of the salivary glands, of which 119 were parotid, 15 submaxillary and but one sublingual, which is herewith reported

The history of the patient herewith reported is reminiscent of that of Brunschwig<sup>2</sup>—a woman, age 60, who died with extensive local destruction of the floor of the mouth and mandible and metastases to lungs and pleura due to a mixed tumor The original growth in the right sublingual gland had been removed 19 years previously

Brunschwig, when he published the case cited above, in 1930, had been able to find but two others in the literature up to that time, which seemed to him to be properly authenticated Since then a number of cases have been reported, as summarized in Table I

TABLE I

SUMMARY OF REPORTED CASES OF MIXED TUMORS OF THE SUBLINGUAL GLAND

Author	Malignant	Recurrent	Benign	Not Stated	Total
Brunschwig <sup>2</sup>	1		2		3
Greenberg <sup>3†</sup>				1	1
Patey <sup>4</sup>		1			1
Eschweiler <sup>5</sup>	1				1
Ahlbom <sup>6</sup>	1		1		2
Vergoz and Salasc <sup>7</sup>			1		1
McFarland <sup>8</sup>		1			1
Smith	1				1
	4	2	4	1	11

† Although Greenberg's<sup>3</sup> article appeared one year before that of Brunschwig,<sup>2</sup> the reference in the Quarterly Cumulative Index appeared some time afterward, it is, therefore, included

The frequency of occurrence of mixed tumors of the sublingual as compared to those of the other salivary glands may be judged from the statistics in Table II

Case Report—E C, female, white, married, age 31, was admitted to St Luke's Hospital in March, 1924 Three years previously, she had noted a swelling in the floor of the mouth which had been lanced on several occasions Examination revealed a nodu-

\* Presented before the New York Surgical Society, May 11, 1938 Submitted for publication August 4, 1938

TABLE II

## COMPARATIVE INCIDENCE OF MIXED TUMORS OF THE SUBLINGUAL AND PAROTID GLANDS

Greenberg <sup>3†</sup>	1 of 30	Ahlbom <sup>6</sup>	2 of 202
Patey <sup>4</sup>	1 of 45	McFarland <sup>8</sup>	1 of 297
Chen and Loucks <sup>9</sup>	0 of 37	Shore (St Luke's)	1 of 135
Martin and Elkin <sup>10</sup>	0 of 24		

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 6 of 770 = 0.8 per cent

lar thickening of the right sublingual gland, which was removed through an incision in the floor of the mouth. The operative diagnosis was chronic inflammation of the gland, but the pathologic examination showed a mixed tumor, presumably of the sublingual gland, although no normal gland tissue was found in the sections (Fig 1).

About four years later, June, 1928, she was again operated upon for a local recurrence. A second recurrence was not long in making its appearance, and she was readmitted to the hospital a third time, in December, 1929, at which time there was present a hard, irregular mass, 2.5 cm in diameter, attached to the mandible. Roentgenologic examination showed bone involvement of the right side of the jaw close to the symphysis.

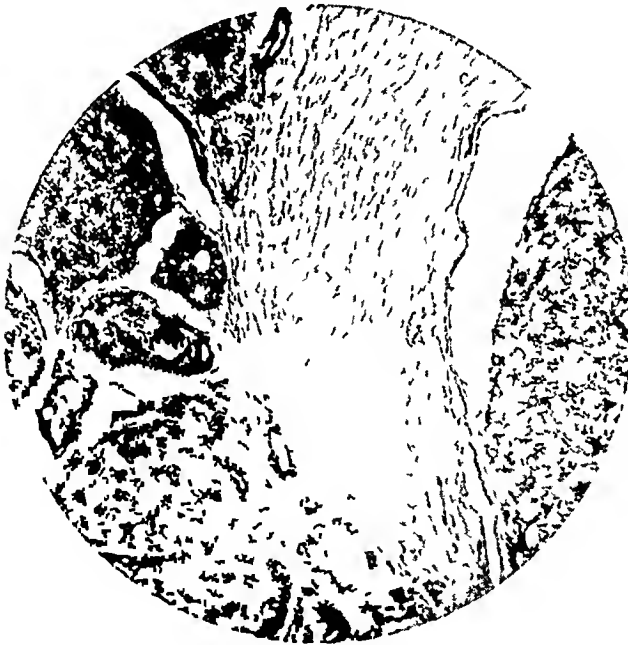


FIG 1—Photomicrograph of mixed tumor of the sublingual gland

The chest was negative. At operation, the mandible was split and the floor of the mouth on the right side dissected out including periosteum and underlying bone at the site of attachment of the tumor. The pathologic diagnosis at this time was adenocarcinoma of the sublingual gland, recurrent. The morphology was the same as that of the tumor previously removed. There was bone and muscle involvement.

In August, 1932, she was again seen at the hospital. Examination showed a small, hard swelling on the left side and two on the right side, below the mandible. A roentgenogram disclosed disease in the jaw bone. Further surgery was considered inadvisable and she was referred to the Radiotherapy Department where she has been under treatment ever since. During the period through 1936, she received an average of 2,000 r per year. This was increased to 5,000 r in 1937. Thus far in 1938, she has received 1,600 r.

# MIXED TUMORS OF SUBLINGUAL GLAND

In October, 1937, she reported that there had been considerable pain in the jaw for two months and a discharge from the floor of the mouth. The chin was swollen and reddened. Roentgenologic examination of the chest showed metastases in the lungs, although there were no pulmonary symptoms (Fig 2).

During the past winter the mandible sequestered, with relief of pain and healing of the sinus. In the past few weeks, however, pain has appeared in the left side of the chest, which may be due to the pulmonary or pleural metastases. There is induration and thickening of the floor of the mouth but no lymph node involvement. The patient's general condition is fairly good. She is thin, but only six pounds under her usual weight. (This patient is included in the series of cases forming the basis of Dr W F MacFee's paper on 'Malignant Tumors of the Salivary Glands' ANNALS OF SURGERY, 109, 481, April, 1939.)



FIG 2—Roentgenogram showing metastases to the lungs from a mixed tumor of the sublingual gland, 13 years after first operation.

Points of interest in this case are (1) The location of the original tumor, which, although not absolutely proved, seems from the evidence to be reasonably attributable to the right sublingual gland, (2) the duration of the disease, now 17 years, (3) the absence of demonstrable lymph node involvement, (4) the pulmonary metastases, and (5) the restriction of local growth since beginning roentgenotherapy, almost six years ago.

## SUMMARY

A case of mixed tumor, presumably of the right sublingual gland, which has proven clinically to be of a low grade of malignancy, is presented. The

patient is alive, with pulmonary metastases, 17 years after the tumor was first noted. The recent literature has been reviewed and 11 cases of mixed tumor of the sublingual gland, including the one reported, assembled. Four of these were malignant. The incidence of sublingual among salivary gland mixed tumors is 0.8 per cent.

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## ESOPHAGOGASTROSTOMY FOR CARCINOMA OF THE ESOPHAGUS

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ONE of the most interesting and important chapters in the development of gastro-intestinal surgery is that dealing with the esophagus and cardiac portion of the stomach. This part of the gastro-intestinal tract has, from many angles, defied surgical attack. First, because a transpleural exposure was imperative. With the development of a technic placing intrathoracic surgical procedures on a sound basis, plus modern methods of administering anesthesia, the first strategic point has been attained. Second, the absence of a serous coat to the esophagus, once it has been freed from its retropleural, or mediastinal location, has made anastomosis for reestablishing the continuity of the gastro-intestinal tract a hazardous procedure. The fact that this difficulty has been overcome in a few successful cases is a source of great encouragement. It is, therefore, predictable that this technic will soon become perfected and standardized, placing the operation on an acceptable basis. Third, a further difficulty that has prevented an otherwise successful issue is postoperative mediastinitis. This, too, in some cases, has been overcome by a simple surgical principle, namely, meticulous care in freeing the esophagus and making no effort to close the space after mobilizing the necessary portion, plus adequate drainage.

The accomplishments of Lilienthal,<sup>3</sup> Garlock,<sup>7</sup> Eggers,<sup>5, 8, 11</sup> Adams,<sup>9, 10</sup> Marshall,<sup>12</sup> Brunn,<sup>6</sup> Ohsawa,<sup>13</sup> Penberthy and Benson,<sup>14</sup> and others have added materially to the development of a sound technic and have stimulated interest in this most difficult problem. At present, the surgeon's greatest handicap, in successfully dealing with these cases, is the tardiness with which they are brought to his attention, or the Chauvinistic complex from previous experience, making palliative treatment seem preferable. It is only by the publication of exact and true statements of efforts in this direction that this handicap can be eliminated. Under present conditions it seems worth while, therefore, to report the appended case in detail.

**Case Report**—Hosp No 205-505 C T, female, age 46, was admitted to the New York Hospital, May 27, 1938, with the history of having first noted difficulty in swallowing certain foods in November, 1937, accompanied by a considerable loss of weight and strength. A diagnosis of a lesion at the esophageal-cardiac junction was made after roentgenologic examination (Fig 1). Radical treatment, however, was not advised. In April, 1938, the symptoms had greatly increased, and loss of weight and strength were progressive. She consulted Doctor Prewitt, who hospitalized her in the Park East Hospital, April 26, 1938, Case No 24533. Preoperative treatment was immediately instituted. Not only had there been a loss of 15 pounds in weight and the development of a moderately severe secondary anemia but, as in all cases of stricture of the esophagus,

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the stomach had become so contracted that it held but four ounces. A Levine tube was passed through the nostril, and regular feedings of a balanced diet, including a proper vitamin content, were administered. The quantities given with each feeding were gradually increased, not only to restore the patient's physical condition, but also to dilate the stomach to a more normal size, so that a sufficient amount of the viscus could eventually be delivered into the left thorax to permit resection and anastomosis without ten-

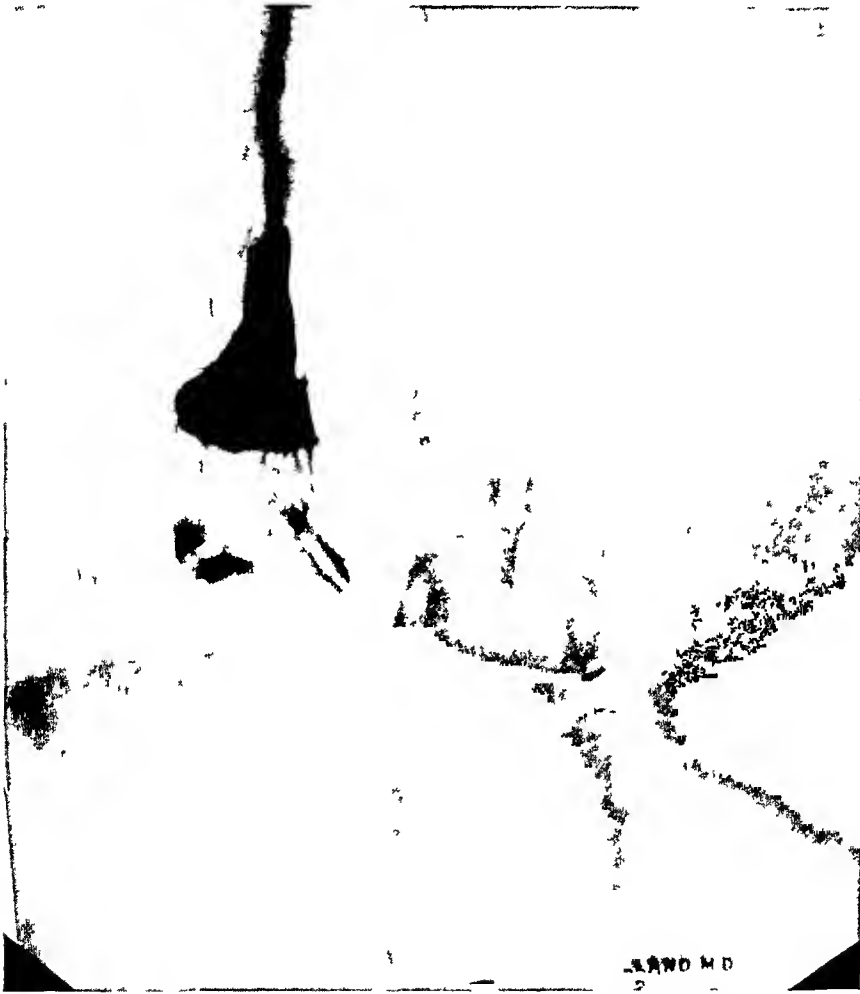


FIG 1.—Roentgenogram showing slight dilatation of the lower esophagus with the greater amount of tumor tissue in the stomach just below the esophagus

sion. The patient was gradually forced to take 6,000 calories per day in repeated 10 ounce feedings. The weight return and the redilatation of the stomach was a slow process.

When admitted to the New York Hospital, the patient appeared well nourished, blood count normal, Wassermann negative. Weight 106 pounds, a loss of 10 pounds from her greatest weight. Her stomach would receive 10 ounces without causing undue discomfort.

*Operation*—June 5, 1938, Doctor Bohrer. Anesthesia was induced with a basal dose of avertin supplemented by intratracheal cyclopropane and oxygen, by Dr. George van Gilluwe, there was good relaxation and the anesthetic was well tolerated. An eight-inch incision was made over the left eighth rib from the angle forward (Fig 2). A left pneumothorax had been induced 10 days preoperatively and there was no disturb-

## ESOPHAGOGASTROSTOMY

ance of pulse or respiration when the rib was resected and the thorax opened. The left pulmonary ligament was divided, allowing the lung to retract from the operative field. No metastatic nodes could be palpated in the mediastinum. A hard mass could be felt through the diaphragm in the region of the cardia.

A four-inch radial incision was then made through the left diaphragm, starting one inch lateral to the hiatus. Through this incision the operator was able to palpate and explore the abdominal viscera. The tumor was estimated to be three inches in diameter. No enlarged nodes were felt in the gastrohepatic omentum. The tumor was not adherent, the liver was normal to palpation. The ligament of Treitz was located and a long loop of jejunum was easily delivered through the diaphragmatic wound. When the examining hand was removed, the spleen herniated through the incision. The abdominal viscera were easily reduced and could be held in place by a small pad. The phrenic nerve was located and blocked with novocain. An incision was made over the esophagus

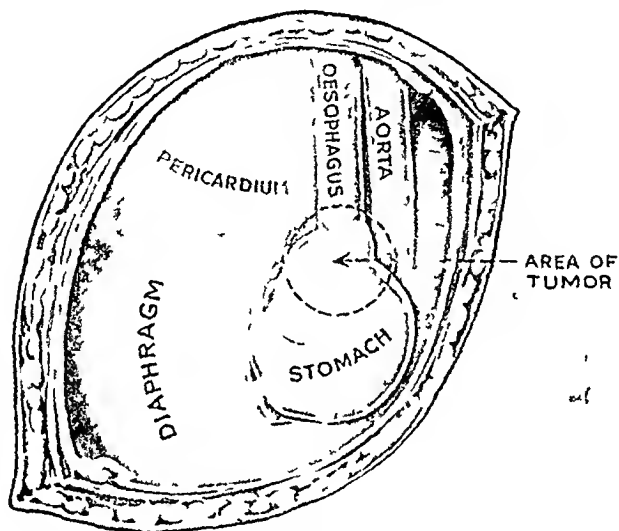


FIG 2—Thoracic cavity opened over the site of the eighth rib. Esophagus has been mobilized, diaphragm incised and stomach delivered into thoracic cavity.

and four inches of it were mobilized from the mediastinum. A gauze pack was immediately introduced into this space to prevent bleeding and protect the space from being soiled. The diaphragmatic incision was carried down through the hiatus, allowing the operator to free the entire lower four inches of the esophagus. At this stage of the dissection the vagus nerves were observed, together with the plexus about the esophagus and upper stomach. It was necessary to divide the left vagus. The most difficult part of the operation was experienced in clamping and dividing the left half of the gastrohepatic ligament and the division of the coronary artery. This, however, was accomplished without accident and the tumor and cardia were delivered into the thorax. Due to the contraction of the stomach, it was difficult to deliver a sufficient amount of it to allow complete removal of the tumor and permit an anastomosis of the esophagus to the stomach. The original plan had been to close the stomach aperture, made by resection of the tumor, then roll the greater curvature up to the cut end of the esophagus and make a small incision to fit the size of that viscus on the anterior gastric surface. The small size of the stomach, however, would not allow this procedure. The tumor, therefore, was resected, and starting at the greater curvature, the stomach was closed down to an aperture just large enough to permit anastomosis with the esophagus (Fig 3). The anastomosis was made with a very fine, curved intestinal needle, carrying a fine silk thread. Two layers of interrupted sutures were used. A careful approximation of the mucosa was accomplished. The posterior suture line was reinforced by a fat pad

covered with pleura that is usually found at the diaphragmatic-mediastinal angle. The anterior suture line was reinforced by a third layer of stomach to the esophagus. The esophageal wall was a firm, thick layer of longitudinal muscle. There was no trouble in approximating the surfaces and no tearing of the muscle by the suture occurred. When completed, the anastomosis appeared strong, there was no tension, and it seemed perfect. The packing was removed from the mediastinum, no bleeding was observed and no attempt was made to close it.

The peritoneal cavity was closed by interrupted suture of the cut edge of diaphragm to the stomach. A siphon drainage tube was introduced through an intercostal stab wound and the thorax was closed in the usual manner. The patient was given 1,000 cc of saline solution and 500 cc of citrated blood during the three hour operation. She was returned to her room in good condition, there was no secondary shock.

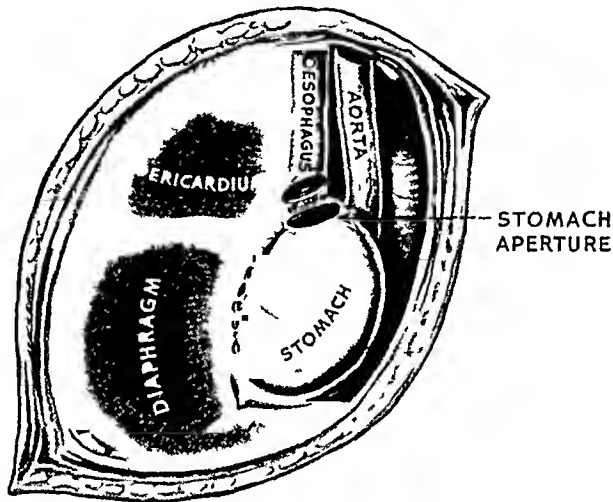


FIG 3—Suture line of stomach after resection. Posterior suture line of esophagogastronomy.

*Subsequent Course*—The first night the patient's temperature reached 101°, remaining below that during the ensuing week. There was a slight amount of serosanguineous drainage during the first 24 hours and none the following day. The Levine tube, which had been passed into the stomach just before the final closure of the anastomosis, was used as a "gas fistula" for the first three days. Later water and food were introduced into the stomach through this tube.

The patient was given 3,000 cc of 5 per cent glucose in saline every 24 hours. However, she developed slight edema of the feet, necessitating a reduction of the saline. Sufficient insulin was administered to prevent glycosuria. There had been no post-operative intestinal disturbance, and no distension or pain. The bowels moved on the fourth postoperative day following the administration of cascara.

On the sixth postoperative day, the patient was permitted to swallow water and a slight drainage around the intercostal tube was noted. The chest was aspirated but nothing was recovered. On the seventh day, some buttermilk was unintentionally swallowed, a fistula was demonstrated to be present, as milk was noted in the drainage. A Witzel type of jejunostomy was immediately performed and all feedings were administered through the jejunum. An interesting intestinal phenomenon then developed. The patient had been moderately constipated preoperatively and during the early post-operative period, but with the introduction of peptonized milk, gruel and similar material into the jejunum, a marked hyperperistalsis was initiated, often resulting in an evacuation immediately after the feeding. This was annoying and troublesome to the

patient, but it was possible, however, to keep her in fair food balance for the ensuing two and one-half weeks by jejunal feeding

Immediately following the development of the fistula, the lower angle of the chest wound was opened for four inches, giving adequate drainage and permitting direct observation of the fistula and anastomosis by introducing a small electric light. This observation was repeated frequently, and it was obvious that the fistula was closing. On the ninth postoperative day, the patient was allowed to sit up in bed, the dressing was removed and she was given water by mouth. About one-half of the fluid intake was recovered through the fistula, but on successive days the quantity recovered became less and less. Charcoal tablets, given by mouth, were, at first, returned through the fistula in considerable amount, later, practically all returned in the stools. On the twenty-sixth postoperative day, she was allowed solid food, a very small amount being recovered through the fistula. On the evening of that day, the patient entertained her family and friends, discussed household details and plans for returning to her home. She was in excellent condition. That night, she received 0.25 Gm of sodium luminal by hypodermic as a sedative. There was considerable "hangover" the next morning but the patient took a small breakfast, was out of bed, and seemed normal except for being sleepy. She returned to her bed at 11 A.M. and under the writer's observation suddenly started muttering, became unconscious, and developed a rapid pulse with cyanosis and dilated pupils. Her condition improved, only to have a second attack at 4 P.M. She expired at 7 P.M. *Clinical Diagnosis* Cerebral embolism. One must, however, question the late effect of sodium luminal, although the patient had repeatedly taken usual doses of phenobarbital without distress.

The untimely death of this patient left unsolved the ultimate outcome of the gastro-esophageal fistula. Judging from its progress up to the time of death, there seemed but one conclusion, namely, complete closure. However, the autopsy disclosed a larger defect in the mucosa than in the muscle wall. The writer believes, however, that it would ultimately have healed completely.

It is interesting to note the slight degree of suppurative pleurisy which developed, and the fact that even in the face of a fistula, no mediastinitis was present. The temperature and pulse curve had been normal for one week prior to her death.

*Pathologic Examination*—*Gross* Doctors Moore and Krumdieck No. 9336. Specimen is the terminal 2 cm of esophagus and proximal 4 cm of stomach. The lumen of the cardio-esophageal angle is markedly constricted and does not permit passage of the little finger. Situated at the angle is a firm, annular tumor mass which completely encircles the stomach and esophagus at this point. Its inner aspect presents multiple discrete and confluent papillary excrescences, zones of ulceration, which give the summit a cauliflower-like appearance (Fig. 4). The tumor infiltrates the wall and extends approximately to a point 2 Mm below the sectioned portion of the esophagus. Distally, the tumor infiltrates approximately 2 cm above the cut margin of the cardia. On section through the tumor there is disclosed a diffusely pearly-gray infiltration in which are noted innumerable lemon-gray granules. The architecture of the region of infiltration is completely obliterated. The gastric mucosa, other than the portion which presents the tumor, shows diffuse hemorrhagic engorgement. There is a small linear, 1 x 0.5 cm, portion of esophageal mucosa which shows no evidence of gross involvement. The serosal aspect of the specimen is nodular. The nodules are flat, and average 2 to 4 Mm in diameter. There are several lymph nodes which show markedly degenerated surfaces on section and which exude a milky substance on pressure.

*Microscopic*—Sections through the tumor masses present widely infiltrating, irregularly anastomosing cords and discrete islands of atypical squamous cells. The cells vary markedly in staining affinity, some present markedly hyperchromatic nuclei, while other nuclei are vesicular and pale. The cells vary markedly in size. There are frequent giant-sized cells found. There is occasional tendency to pearl formation and suggestive

keratinization. The sections also reveal a very prominent degree of necrosis, fibroblastic proliferation and infiltration with young organization tissue, and foci of inflammatory cells. The carcinomatous infiltration is so wide as to completely obscure the basic markings of the section. In no portion, of those areas examined histologically, are the cells of the gastric epithelium recognized. The regional lymph nodes show evidence of extensive involvement by the atypical squamous cells. There are also lymph nodes included in the section which show no metastatic involvement but marked hyperplasia and vascular engorgement.

*Pathologic Diagnosis* Immature, stenosing, annular, ulcerating squamous cell carcinoma

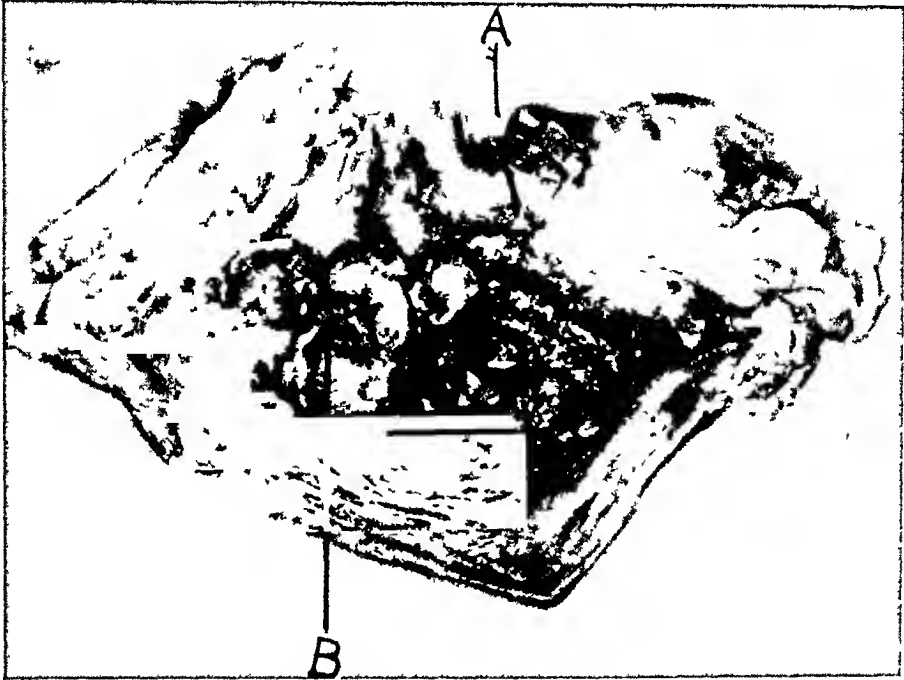


FIG. 4.—Resected specimen of esophagus and stomach cardia. A Constricted esophageal orifice. B Cauliflower mass which completely encircled the esophageal orifice and cardia of the stomach.

noma of the esophagus with infiltration of the stomach and metastatic involvement of the regional lymph nodes.

#### *Significant Autopsy Findings*

(1) At the site of the anastomosis the mucosa had failed to heal by primary union in two distinct areas. Both of these defects communicated with the esophageal fistula leading into the pleural cavity.

(2) There was a very small metastasis to the liver and also to the small lymph nodes in the gastrohepatic ligament.

(3) Sections at the site of the anastomosis showed no tumor cells.

(4) There was a fibrinopurulent pleurisy of the left pleural cavity.

(5) The remainder of the gastro-intestinal tube was normal except that the portion of the stomach lying below the diaphragm was markedly contracted, being one and one-half inches in diameter.

(6) No gross anatomic lesion of the brain was found.

**DISCUSSION**—Several questions naturally present themselves.

(1) Why did the fistula develop, and would it eventually have healed?

- (2) Would the lung have reexpanded after prolonged collapse with an open pyothorax?
- (3) Was it proper to explore through the thoracic route or should the operability have been determined by abdominal exploration?
- (4) What is the physiology of the excessive peristalsis following jejunal feedings?
- (5) Had the exploration revealed metastases to the liver and to local lymph nodes, as described in the autopsy protocol, was resection indicated?

(1) The answer to the first question must, necessarily, be largely speculative. Three facts are definitely known. First, that both stomach and esophagus were viable at the time of the anastomosis, second, meticulous care was taken to approximate the mucosa, third, at the autopsy, no tumor cells were found at the site of the dehiscence. In spite of these facts, the mucosa did not heal per primam. The probable explanation is that the blood supply to the mucosa on both sides had been markedly reduced (a) by the operative procedure, (b) by the slightly angulated position in which they were left after the anastomosis, the stomach being pulled through the diaphragm and the esophagus removed from its normal mediastinal position, (c) a third factor must also be considered, while the Levine tube served admirably as a "gas fistula," the presence of a foreign body in close approximation to any suture line is always objectionable, particularly where the blood supply is questionable. The writer believes, however, the Levine tube was in no small way responsible for this defective healing. A simple gastrostomy would better have served all requirements. The pull of the powerful longitudinal muscles of the esophagus during deglutition (a preoperative fear) could not have had much influence on the mucosal union, as the muscle suture line held satisfactorily. An observation made on the exposed portion of the esophagus by means of the above described electric light demonstrated the marked peristaltic action of this powerful muscle.

By limiting the amount of material passing through the fistula, and not introducing food into the stomach that would stimulate secretion of digestive juices, erosion of the fistula was avoided, from direct observation it is fair to conclude that the fistula eventually would have closed.

(2) At the autopsy, the left lung was found markedly collapsed. It did not crepitate. The visceral pleura was not markedly thickened. It is conceivable that with a closed sterile pneumothorax this lung would have reexpanded. If not, the right lung probably would have hypertrophied and herniated into the left pleural cavity to fill the space. If the pleurisy could not be controlled and a sterile pneumothorax secured, thoracoplasty would have been imperative.

(3) In answer to this question, the writer has a definite belief, namely, thoracic exploration is the route of choice. (a) Contrary to general belief, the thoracic route causes no greater shock than abdominal exploration, but more time is required in opening and closing the wound. (b) Exploration is much more adequate since the thorax as well as the abdomen can be satis-

factorily examined (c) If operable, the incision permits immediate procedure (d) It is more difficult to determine operability by the abdominal route, hence many operable cases would be rejected From present experience, the thoracic route for exploration of operability is by far the more acceptable

(4) The intestinal hyperperistalsis induced by jejunal feeding is an interesting physiologic fact It has been observed many times and seems not to be unusual It is probably the same reaction that is noted when a quart of warm saline is given on an empty stomach to a person suffering from constipation In this instance, the warm solution leaves the stomach at once and when it reaches the jejunum hyperperistalsis ensues followed by evacuation It has also been noted following complete gastric resection when the continuity of the gastro-intestinal tract is reestablished by an esophagojejunostomy In the latter instance, this difficulty is gradually overcome

It will be noted that during the exploratory phase of the above described operation, the jejunum was delivered into the thorax This was done to assure the operator an alternative in case a union of esophagus and stomach could not be made without tension Judging from experimental work on dogs, this would not be a desirable procedure on a human

(5) This, of course, is a debatable question The European surgeon undoubtedly would answer in the affirmative, since the metastases were so small and the original lesion so productive of discomfort Given a small metastatic lesion in a silent area, the writer is inclined to believe that the removal of the primary malignant lesion, where it causes or will cause severe suffering, is the proper course to follow

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# DUODENAL STASIS

## CLINICAL AND EXPERIMENTAL OBSERVATIONS

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DUODENAL stasis, or chronic duodenal ileus, a condition remarkable for the number and variety of clinical symptoms attributed to it, is also one which is variously defined in the literature. This diagnosis is made by some authors when the opaque medium seems to hesitate for several seconds, as it were, before entering the distal part of the duodenum or the jejunum<sup>20</sup>, yet it is known that such delay may occur when the stomach empties rapidly,<sup>2-6</sup> owing, for example, to hunger or to the action of purgatives.<sup>2</sup> Other writers consider that, besides the delay, there should be writhing or pendulum peristalsis which is "quite characteristic of obstruction"<sup>18</sup>, it is known, however, that this type of peristalsis occurs in duodenitis, that it may be found in affections of the gallbladder,<sup>6-7</sup> the pancreas,<sup>6</sup> and the appendix<sup>6,7</sup>, that it is even seen in healthy persons<sup>4-6</sup> in other words, that it does not necessarily indicate obstruction. Taking a more conservative view, duodenal stasis implies widening of, and long lasting retention in, the dependent duodenum<sup>7-9</sup>, but Barclay<sup>2</sup> has found this to occur in people who were not conscious of any disorder, wherefore, he concludes that symptoms might have been ascribed to what is, in reality, a normal but unusual variation of the duodenal mechanism. In its practical consequences, this view differs radically from that of a majority of authors, who advocate medical or surgical treatment, under the assumption that duodenal stasis is the expression of some kind of obstruction.

This divergence of opinions about the clinical significance of a mechanism believed to be pathologic is not surprising if one considers how little is known about the normal physiology of the duodenum, for this segment, which is subject normally to influences from various organs and of various kinds, may considerably alter its function and, hence, its appearance during different phases of digestion. If present descriptions of normal duodenal activity differ, it is probably for this reason, nevertheless, all of the descriptions may be correct, as each may fit one special type or phase of gastric and intestinal digestion—the type of peristalsis varies individually, with the kind and quantity of the opaque meal given, and with certain technical factors of the roentgenologic observation.

*Physiologic Data*—The passage of an opaque medium through any part of the digestive tract is obviously dependent on, and to some extent controlled by, the condition of the adjacent sections. The passage through the duodenum is influenced by the following factors at least. The relation in size and capacity

between stomach and duodenal cap, the liquidity of the gastric contents, the rate of passage through the cap, the condition of the duodenal mucosa, and, naturally, the pyloric mechanism. These factors, again, are made variable by the chemical processes of digestion.

In examinations of 300 healthy students, the following type of duodenal activity has been found to be common, it being understood that in the physiology of digestion there is no such thing as one single normal mechanism. After having passed through the pylorus, the opaque medium remains for a number of seconds in the cap,<sup>1</sup> at the tip of which it seems to become arrested. Incidentally, this is the reason why the cap is so easily visualized in healthy subjects. By a contraction, wave-shaped or more tonic, which proceeds from the tip of the cap towards the pylorus,<sup>3</sup> the opaque medium is then driven into the descending duodenum as though by the action of a bellows.<sup>3</sup> While being thus moved on, the opaque medium is evenly spread over the duodenal mucosa, thereby producing the fragmented or "feathery" aspect of the normal mucosal relief. During this time, the cap may fill again, and the cycle repeat itself, but it is more common for the pylorus not to relax until all or most of the opaque medium has been moved on into the third or fourth duodenal position, either by a "stripping" contraction progressing smoothly from the tip of the cap downward, or by what appears to be the activity of the muscularis mucosae (not, of course, by the activity of the valliculae conniventes, as recently stated<sup>18</sup>).

At the very beginning of gastric evacuation, as well as during its second half, the entire mechanism is less regularly timed than at the period of active gastric peristalsis, the latter being normally most marked about ten minutes after ingestion of the opaque medium. More information on normal physiology can be obtained by giving some opaque medium at different intervals after ingestion of a normal meal containing fat and protein. Provided gastric acidity is normal, very little of the gastric contents passes through the pylorus during the first hour, small amounts accumulate in the cap for considerable periods, up to 45 minutes, after which they pass very rapidly through the entire duodenum. But, after about three hours, gastric evacuation becomes more rapid, and the passage through pylorus and cap is then very similar to that observed about ten minutes after ingestion of plain barium sulphate suspension, though usually somewhat slower. When the cap is small, either congenitally or owing to scars and fibrosis, the opaque medium evacuated during a normal pyloric relaxation overfills the cap, with the result that parts or all of the barium proceed immediately into the dependent duodenum. Similarly, a tonic contraction of the cap, as observed in duodenitis,<sup>12</sup> or motor irritability, as in duodenal ulcer, produces a diminution in capacity of the cap, with similar results. The relation between the cap and the stomach may also be altered in the presence of permanent patency of the pylorus, *e g*, in hunger, or in carcinoma infiltrating the pylorus, and a continuous flow into the jejunum is then not uncommon. When the duodenal mucosa is swollen, various alterations of the passage are observed and frequently associated with pylorospasm, in the absence of



FIG 1—(A) Normal duodenum. Arrest at the tip of the cap, feathery mucosa in dependent part. (B) Duodenal stasis. valliculae conniventes permanently seen. (C) Atony of duodenum during gallbladder colic.

the latter, however, rapid passage through the cap is commonly though not invariably noted.

Increase of fluid in the stomach, both by pathologic hypersecretion or retention and by the physiologic increase which often occurs towards the end of gastric evacuation, is usually associated with very rapid passage through the upper duodenum, provided the pylorus is not spastically closed, but even in the presence of pylorospasm, rapid passage through the duodenum may be observed under favorable conditions during the short periods of pyloric relaxation.

Unpublished experiments with various types of food suggest that the abnormal duodenal peristalsis observed in certain biliary diseases<sup>15</sup> is related to the amount of fat administered with the opaque medium, although the results are not yet conclusive, they are here mentioned as a suggestion that extra-intestinal conditions may at times influence the duodenal mechanism.

In all the conditions above discussed, irrespective of their being physiologic or pathologic, rapid passage through the duodenal cap is often associated with a delay of the passage through the dependent duodenum. The barium which, in these cases, seems to fall through the descending portion, may either collect at the lower duodenal knee (*genu inferius duodeni*), whereby the latter appears to be temporarily somewhat widened, or it may become arrested in the lower horizontal loop (*pars horizontalis inferior duodeni*) by what appears to be a circular tonic contraction. While in the former case, there is, in general, no marked peristalsis, writhing and surging are common in the latter condition. In either case,

the opaque medium is moved on into the jejunum after a period of, say, from two to ten seconds. Excepting for peristaltic waves, nothing changes the aspect of the normal "feathery" mucosal pattern, only occasionally, for a second or two, may the valliculae conniventes emerge, as it were, into the mucosal relief.

*Clinical Observations*—From the mechanism above described, duodenal stasis differs in degree rather than in kind. The widening of the dependent portion persists throughout indefinite periods of observation, the valliculae conniventes are permanently seen in the region of stasis, whereby the normal fragmentation of the medium disappears, and the barium accumulates in a pool for periods extending over hours. In the upright position this pool may be smoothly outlined, the valliculae appearing to be flattened out by the weight of the stagnant opaque medium; but in recumbency, when the duodenum is less overfilled at one place, the valliculae are recognizable either in relief or

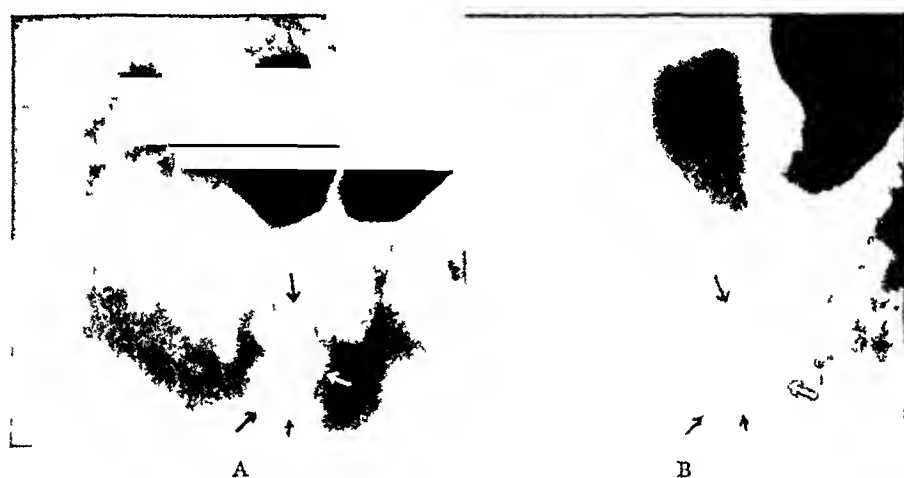


FIG. 2—A and B Duodenal cycle in an instance of tumor of horizontal portion (arrows). Note absence of retention.

at least, by the regular indentations they produce in the duodenal contour. Increased or abnormal peristalsis, such as writhing, churning, and surging, may or may not be noted, if present, it is usually more pronounced in the recumbent position.

According to present views, duodenal stasis signifies, in a majority of cases, obstruction of the duodenum by some anatomic process. Intrinsic growth, compression by extrinsic tumors, kinking by periduodenal adhesions, compression by the superior mesenteric vessels (arterioesenteric occlusion), and megaduodenum.

(1) *Intrinsic Growth*—This is very rare.<sup>2</sup> In a case of annular tumor recorded by Barclay,<sup>2</sup> retention and dilatation of the duodenum cephalad to the growth were very marked. The author has seen two cases, but neither of them was verified by operation, there was no stasis (Fig. 2).

(2) *Extrinsic pressure*—Twelve cases of pancreatic tumors (seven verified) and eight cases of various growths causing displacement of, or pressure upon, the duodenum, were studied for duodenal stasis. The duodenal curve was found widened in 11 tumors of the pancreas, the duodenum was flattened

and its lumen slit-shaped in the same 11 cases, and in one case of an enormous right hydronephrosis containing 11 liters of fluid, there seemed to be no flattening in one pancreatic tumor and all the other tumors, retention in the duodenum was found in two cases of pancreatic tumor with flattened duodenum and in one case of retroperitoneal sarcoma, in both of which the valliculae conniventes were permanently seen, but in all the other instances, there was neither retention nor persistence of valliculae, the duodenal relief showing normal segmentation. Hence, there was duodenal stasis in three out of 20 cases of extrinsic compression (15 per cent).

(3) *Periduodenal Adhesions*—There are two distinct groups (A) Adhesions in the upper duodenum due to ulcer, (b) adhesions in the duodenum distad to the cap, *e g*, to the liver and gallbladder or towards the colon. Only such cases have been analyzed in which adhesions were unquestionable owing to the immobility, deformity, or angulation they produced. Fifteen cases of Group A, and seven of Group B were studied. Briefly, the results are as follows. No duodenal stasis was found in Group B, stasis was present in five cases of Group A, in all of the latter, the passage through the cap was rapid—three times in the presence of an active duodenal ulcer with crater, and twice in the presence of a pipe-shaped deformity of the cap.

(4) *Anteromesenteric Occlusion*—This is held to be due to pressure upon the duodenum by the superior mesenteric vessels, when the angle formed by the aorta and these vessels is lessened, and when there is tension on the mesentery owing to visceroptosis. The acute form occurs as a rule in patients too seriously ill to allow extensive roentgenologic studies. In three cases, where the clinical symptoms and signs suggested this condition, roentgenologic examination showed permanent atony and dilatation of the stomach, with no filling of the duodenum, in two of them, autopsy failed to reveal the presence of any kind of obstruction. This is in accord with observations published by German authors.<sup>13 10</sup> In the chronic or intermittent form, the roentgenologic findings described in the literature are those of duodenal obstruction, that is, according to the foregoing, indirect, untypical, and ambiguous signs. With an adequate technic, however, the presence of so serious an obstruction should be revealed by the more tangible "direct" roentgenologic signs—in obstruction by a rather large vessel, the filling defect caused by its pressure should be demonstrable. Such a defect, at the left border of the spinal shadow, has been found in four of our cases of duodenal stasis. In two of them, however, there was an active duodenal ulcer, and stasis disappeared when the crater had grown smaller. In the third instance, a woman with amebic colitis, examination in various diameters showed that the fourth part of the duodenum was located much more anteriorly than could be expected in the instance of compression by the mesenteric vessels, and in the fourth case, the defect was so variable in size and localization as to suggest tonic contractions rather than an anatomic compression.

(5) *Megaduodenum*—Two cases have been seen, in one, a child who died of dysentery, no roentgenologic examination was made, no obstruction was found distad to the enlargement on autopsy. In the second instance, a stout

woman, age 37, stasis was more pronounced than in any other instance observed by us, after passing normally through a cap of average size, the opaque medium collected at the lower duodenal knee, in a pool about one-third the size of the stomach, and it moved on merely by flowing over the level of the pool. The latter remained visible as an isolated filling after the entire tract had emptied itself. No mucosal pattern was demonstrable and



FIG 3—Pipe shaped deformity of cap due to chronic ulcer (confirmed). Stasis in dependent duodenum with permanence of valleculae conniventes (arrows). No obstruction of the third and fourth portions of the duodenum was found at operation.

there was no peristalsis in any part of the duodenum beyond the cap. When the patient was lying on her left side, the barium easily entered into the jejunum. At operation, the diagnosis was confirmed and no obstruction was found. This observation does not conform to the statement that megaduodenum occurs in hyposthenic persons, that the cap is involved in the dilatation, and that the mucosal pattern is normal.<sup>18</sup>

(6) *Duodenal Stasis in Diseases of Other Organs*—In over 2,000 examinations reviewed, duodenal stasis was recorded in the following instances

Jejunitis, two cases, jejunal ulcer after gastro-entrostomy without obstruction of the afferent loop, one, cancer of prepyloric region with permanent patency of the pylorus, two, starvation with rapid gastric evacuation and permanent patency of the pylorus, two, gastritis with hypersecretion, three, biliary colic during examination, one case. In the cases of permanent patency of the pylorus, the entire duodenum was continuously overflowed with barium, in those with gastritis, the passage through the duodenal cap was accelerated, but in the cases with jejunitis and jejunal ulcer and in the case with biliary colic, neither of these mechanisms was observed. In active

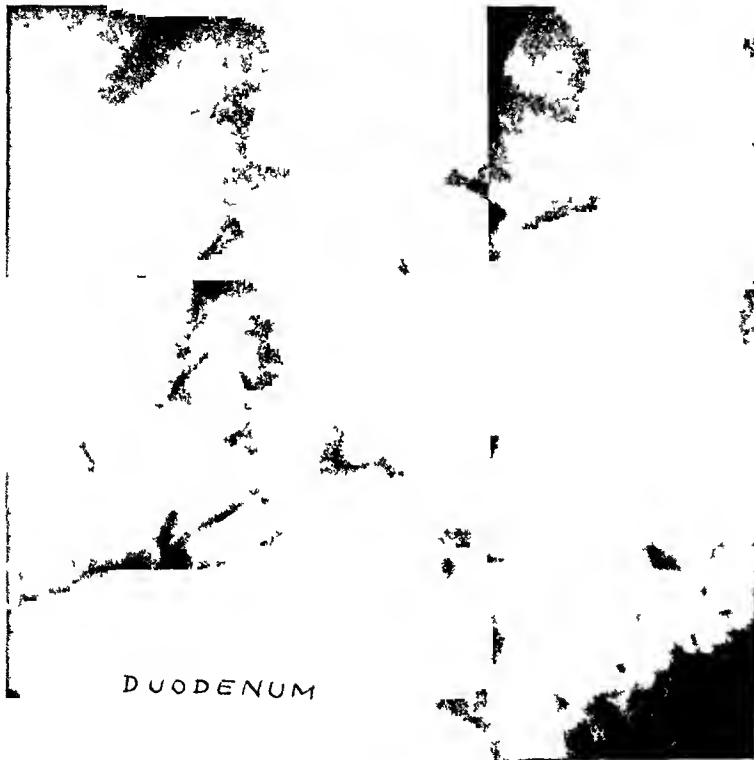


FIG 4—Duodenal stasis in active ulcer of posterior wall of cap

duodenal ulcer, duodenal stasis is inconstant. Statistical data would not reveal the real relation, for the development of duodenal stasis in these cases depends upon a variety of interrelated functional disorders rather than on the size or localization of an ulcer. In duodenal ulcer, stasis seems to occur more commonly when there is no pylorospasm.

(7) *Acute Angulation of the Duodenojejunal Flexure*—Among 100 cases selected at random, an especially acute angle of the duodenojejunal flexure was found in 18 instances, there was no stasis.

(8) *Duodenal Stasis in Intestinal Atony*—Two cases were observed in which duodenal stasis alternated with atony of the upper small intestines. These patients had vague abdominal symptoms, the clinical findings were not significant. The condition observed suggests some type of disordered nervous control.

*Experimental Findings*—Experiments were made with the object of studying (1) The interrelations between duodenal stasis and the rate of passage through pylorus and cap both in normal and pathologic conditions, (2) the possible production of duodenal stasis by abdominal pain

(1) A Three men with apparently normal stomachs and duodenum were given 200 cc of the usual barium sulphate suspension. Gastric and duodenal evacuation was found to be normal. After ten minutes, each was given the yolks of three eggs. In one person, this had no effect upon the passage through stomach and duodenum, but in the duodenal mucosa transverse rugae appeared in which the barium seemed to be "caught" (Fig 5). In the two other persons, the pylorus closed a few minutes after ingestion of

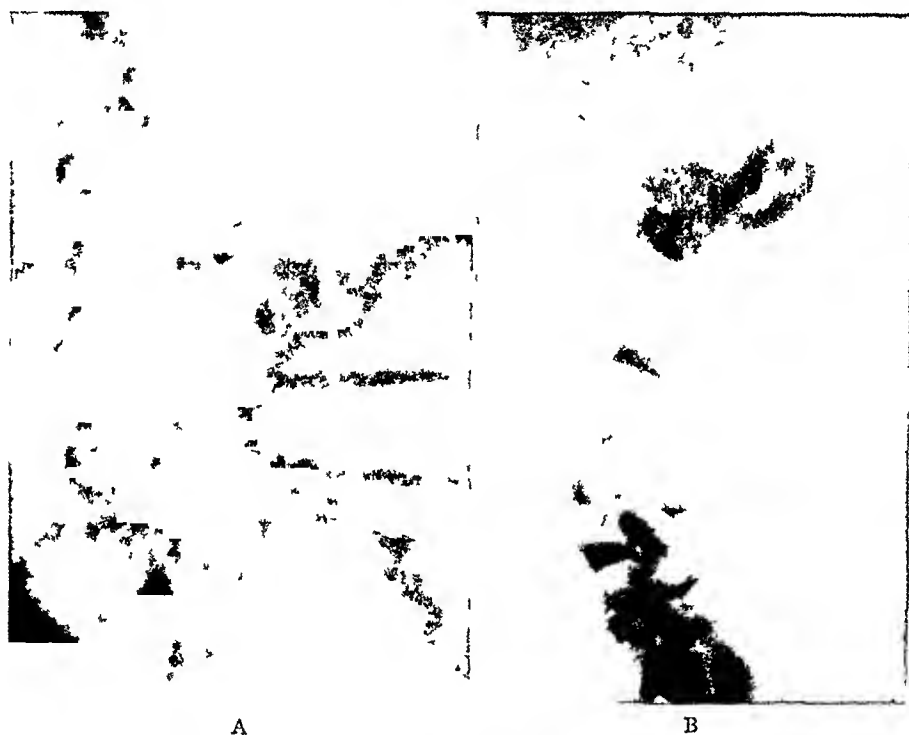


FIG 5—Mucosal relief. (A) After ingestion of plain barium suspension. (B) Twelve minutes after additional ingestion of egg yolks, the opaque mixture is "caught" in transversal rugae which have formed in the meanwhile.

the egg yolks, the stomach enlarged slightly by loss of tone and gastric peristalsis slowed down. No opaque medium having been seen passing through the pylorus during the subsequent 25 minutes, 1/50 grain of atropine was injected subcutaneously. After seven and 12 minutes, respectively, the pylorus relaxed, the barium passed rapidly through the cap, but each portion which passed through the pylorus was retained at the lower duodenal knee for periods varying between three and 12 minutes. The valliculae coniventes were not distinctly seen, as the admixed secretion veiled the mucosal relief. There was no discomfort and no other symptoms whatever.

(1) B Three patients with well-marked pylorospasm but without demon-

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\*It is known, of course, and had been verified in numerous examinations, that atropine medication does not, in itself, induce duodenal stasis.



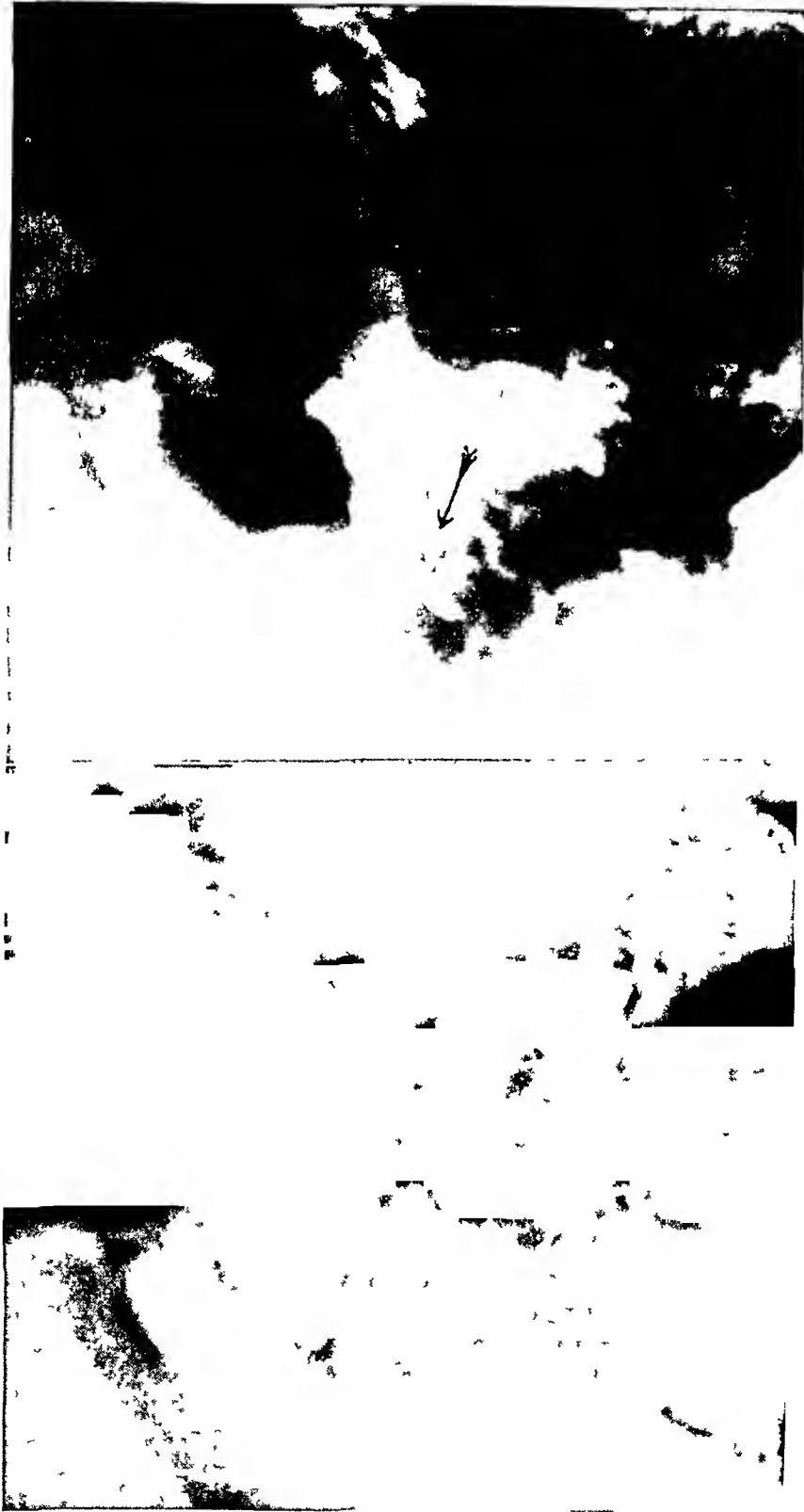


FIG 6—Pyloric contraction following addition of egg yolks to the opaque medium (A) Twelve minutes after ingestion of eggs (B) Twenty minutes later after injection of atropine the pylorus has relaxed, there is well marked duodenal stasis The arrow points to the papilla of Vater

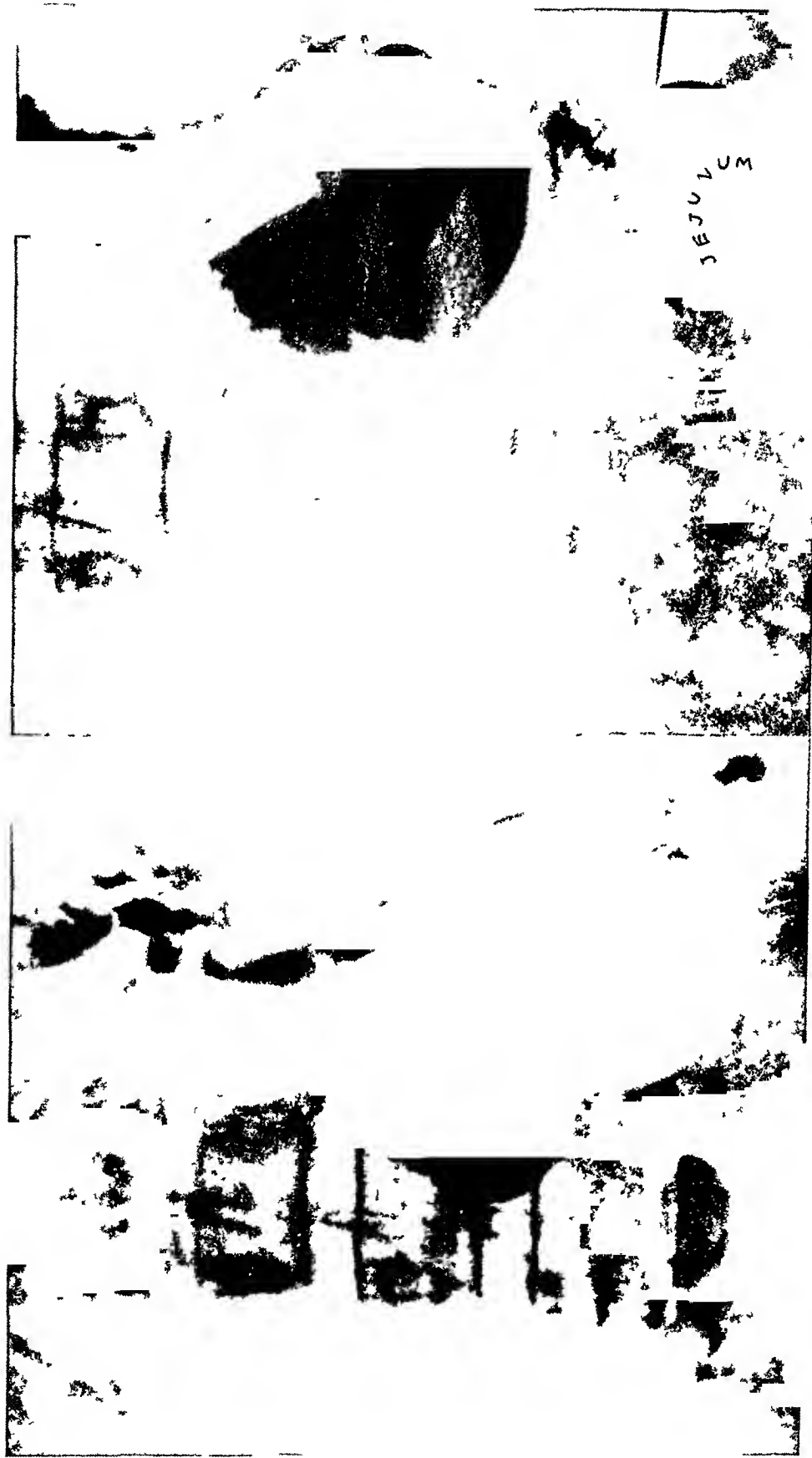


FIG. 7—(A) Twenty minutes after ingestion of barium. Severe pylorospasm. (B) Three hours later, pylorospasm still present although some barium has passed on into the jejunum. Note entire absence of any barium in the duodenum.



FIG 8—Same case as shown in Figure 7 (A) Twenty five minutes after injection of atropine, pylorus open, stricture almost empty, pronounced duodenal stricture (B) Three hours later

## DUODENAL STASIS

strable lesion of stomach and duodenum were examined before and after atropine medication. The first, a young woman with amebic colitis, showed marked gastric hypersecretion and pylorospasm lasting for more than three hours, no barium could be pressed through the pylorus. Thin streaks of barium, not visible on fluoroscopy, were discovered on roentgenograms on which they were found spread over various intestinal loops at four hours, but during this time, the duodenum was passed so rapidly that neither the cap nor the distal parts could be seen. The following day, examination was



FIG 9—Same case as shown in Figures 7 and 8. Three and one half hours after injection of smaller dose of atropine. Pylorospasm, slight duodenal stasis. The series illustrated in Figures 7, 8, and 9 shows the experimental production of duodenal stasis with almost quantitative pharmacologic results.

repeated after hypodermic injections of atropine, 1/50 grain 12 hours before examination, and another 1/50 grain 20 minutes before it. The pylorus then opened a few minutes after barium had been given by mouth, barium passed so rapidly through the cap that the latter could not be seen distinctly, it then accumulated in the dependent duodenum where it was retained during the subsequent four hours (Fig 8). The patient stated that she felt no discomfort whatever. After two days, examination was repeated without atropine medication, and the findings were identical in every respect with those observed the first day. Again, 48 hours later, only 1/100 grain of

atropine was injected 20 minutes before examination, pylorospasm was less marked, some barium passed through the duodenum, and slight retention occurred at the lower duodenal knee (Fig 9). In the second patient, severe pylorospasm having been found on a routine examination, injection of 1/100 grain of atropine resulted in normal gastric evacuation with arrest of the barium at the tip of the cap, there was no duodenal stasis. A second injection of 1/100 grain, made 35 minutes later, induced definite retention in the dependent duodenum, the barium passing through the cap without arrest at its tip. There were no symptoms. In a third patient, examination was made, first, without atropine, then, 50 minutes later, after injection of 1/100 grain, and finally, after 24 hours, after injection of 1/50 grain. There was pylorospasm on the first examination, normal passage through the cap with arrest at its tip on the second one, and very rapid passage through pylorus and cap with slight retention in the dependent duodenum on the last examination, in the entire absence of any symptoms.

(2) As previously reported,<sup>16</sup> transient atony of the intestines may result from abdominal colic, both spontaneously or artificially produced, *e g*, by distention of the renal pelves. In two patients of this group, the left renal pelvis was distended by retrograde pyelography, barium having been given by mouth 20 minutes before. There was severe colicky pain, complete atony of the colon and upper small intestines, and tonic contraction of pylorus and in ileal loops, lasting in both cases for more than seven hours. In both instances, the dependent duodenum was widened during this period, and the opaque medium was retained in it for about three hours. Both one day before and one day after the experiment, the entire digestive tract was normal in the two patients. Widening and atony of the duodenum were also seen in one case of biliary colic, as above described (Fig 1C).

DISCUSSION.—In the series here reported, duodenal stasis with well-marked retention was comparatively rare in anatomic obstructions, but more common as a result of, what appears to be, a reflex mechanism. The observations would seem to indicate that duodenal stasis occurs. First, when the passage through pylorus and cap is accelerated, and secondly, when there is a lesion in the jejunum. Normally, two valves, the pylorus and the tip of the duodenal cap, control the flow from the gastric reservoir into the small intestines. When their action is impaired either anatomically or, *e g*, by atropine medication, the dependent duodenum may in some instances act as a third potential valve which delays the passage into the jejunum. As a potential mechanism, this is not constant. As far as we know, this valve is not a preformed sphincter, but, by atony, as well as by a tonic contraction in the horizontal portion, a retardation of the flow occurs, which seems to make up for accelerated passage through pylorus and upper duodenum.

The compensatory action of potential valves is nothing unusual in the physiology of the digestive tract in man. For instance, when the hepatic flexure is smoothly rounded, the cecocolonic sphincter is frequently well developed or contracted, and, vice versa, when the hepatic flexure is kinked, the

sphincter may not be seen distinctly. Similarly, retention in cephalad parts is known to occur when distal segments are diseased, *e g*, that pylorospasm occurs in lesions of the ileum, cecum, and colon. It may be that this type of retention represents a kind of protective mechanism which prevents flooding of irritated loops.

In this series, duodenal stasis was unexpectedly found to be rare in instances of anatomic compression and in kinking of the duodenum. This is at variance with other reports on the subject, but is in accord with observations on obstruction in other parts of the intestines. It is well known that sharp kinks, and unusual positions, rarely impair normal function,<sup>2 3</sup> and that there has to be a considerable amount of compression or stenosis before dilatation and retention become definite. On the other hand, spasms and atony often interfere distinctly with the passage. Ileal stasis for instance, a condition much discussed in the past, is decidedly rare in the presence of extensive perityphlitic adhesions, and even more so in obstructive tumors of the cecum, but it is less uncommon in inflammatory conditions not associated with stenosis, where it seems to be due to reflectoric inhibition of the passage. It is not here denied that acute obstruction of the duodenum by a mesenteric vessel may occur, but the question is raised whether the diagnosis of chronic, recurrent, or intermittent arteriomesenteric occlusion is built on firm ground. As above mentioned, the conventional roentgenologic signs of duodenal obstruction are indirect and ambiguous. But the clinical signs are not characteristic either—vomiting relieved in the genupectoral position, one of the cardinal symptoms, has been found by us in verified cases of hydrops of the gallbladder, acute pancreatitis, duodenal ulcer, renal calculi—in all of which cases it did not recur after surgical treatment of the underlying lesion. It is difficult to see why migraine, another disorder ascribed to duodenal stasis, should be the result of arteriomesenteric occlusion when it occurs in hyposthenic women over 30 years of age,<sup>18</sup> while it is admittedly independent of it in stout persons, moreover, in migraine neither vomiting nor the “toxic” symptoms are relieved by or in the genupectoral position. In extensive studies on the relation of migraine to various extrinsic factors, the author has hitherto failed to see a patient in whom duodenal stasis was present during the attack.

The third part of the duodenum is quite movable and slides back easily in the supine position, pressure upon it by the spine is very common during examinations in recumbency, but in no instance have clinical symptoms been observed by us under these conditions, even when the pressure by the spine caused well-marked delay of the passage. Anatomically, nothing is known about the spatial relation between the mesenteric arteries, aorta, and duodenum in healthy persons of the hyposthenic type during operation—that is, under the influence of anesthetics, operative shock, and opening of the abdominal cavity, factors known to profoundly affect the position and shape of the intestinal organs. Therefore, in regard to the angle formed by a movable vessel and its influence upon a hidden intestinal loop difficult to approach,

it seems somewhat doubtful whether operative findings, that is, observations made under quite unphysiologic conditions, can be accepted as conclusive proof. One may ask whether the conception of arteriomesenteric occlusion is not an example of what Barclay has called the persistent attempt to make the viscera conform to the pattern of the dead. One may also ask whether perhaps this occlusion is not another "Lane's kink," that is, an abnormality not verifiable by the most experienced observers.<sup>2</sup> Many of these alleged anomalies are, in reality, normal conditions, Barclay has conclusively shown that they often represent individual variations, and the author has previously pointed out that they may also correspond to physiologic changes occurring during digestion.<sup>3, 16</sup> These two views are complementary, in the matter here discussed, both methods of approach demonstrate that duodenal stasis may be unnoticed by the person in whom it is observed; hence, that it is not synonymous with disease.

We are, therefore, forced to the conclusion that the roentgenologic demonstration of duodenal stasis is not, in itself, sufficient to warrant the diagnosis of obstruction, since the finding does not even prove that the clinical symptoms are due to duodenal stasis. In a majority of cases, duodenal stasis is a compensatory mechanism, not characteristic of any particular disease. From this reflectoric condition, anatomic obstruction is to be distinguished by the presence of the "direct" roentgenologic signs of stenosis or compression.\*

#### SUMMARY

(1) In this series, duodenal stasis was found to be rare in anatomic obstructions such as compression by extrinsic tumors, fixation by adhesions, kinking, and intrinsic growth. Excessive stasis was present in one case of mega-duodenum.

(2) Both in physiologic and in pathologic acceleration of the passage through the pylorus and duodenal cap, duodenal stasis is common. In the presence of pylorospasm and of physiologic pyloric contraction, duodenal stasis could be produced by atropine medication, if this caused the pylorus to relax. Abdominal colic, spontaneous or experimentally induced, may also cause duodenal stasis.

(3) Observations on jejunitis and on permanent patency of the pylorus, and experiments in man, suggest that duodenal stasis may occur as a compensatory or as a "protective" mechanism when the food passes through the proximal duodenum too rapidly.

(4) The pathogenesis and incidence of arteriomesenteric occlusion are questioned.

(5) Duodenal stasis was observed to occur in the entire absence of clinical symptoms. Clinical symptoms, allegedly typical of duodenal stasis, were found in diseases of an entirely different nature. Hence the presence of

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\* Duodenal stasis due to anatomic obstruction will be discussed in a separate report (in collaboration with P. F. Sahyun)

duodenal stasis, as demonstrated roentgenologically, neither indicates anatomic obstruction, nor proves that the clinical symptoms are due to duodenal stasis

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## MORBIDITY FOLLOWING CHOLECYSTECTOMY

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THIS COMMUNICATION records a critical analysis of patients returning to the Follow-Up Clinic of the Hospital of the University of Pennsylvania, from one to four years after cholecystectomy, with symptoms indicating that the operation had not given them the relief which either they or their surgeon anticipated. The cases were selected from a larger series, of 504 patients with gallbladder disease, operated upon on the service of Dr. E. L. Eliason, during the 12 years from 1922 to 1934. Various aspects of this complete series, including mortality, type of pathology encountered, and operative technic, have recently been reported by Eliason and Erb.<sup>2</sup> The present discussion is not concerned with such factors as these, nor with anatomic defects, such as postoperative hernia, wound infection or fistula, but only with unsatisfactory functional end-results. Moreover, since the inadequacy of cholecystostomy as compared with cholecystectomy is well recognized, we will confine ourselves to the results after the latter procedure.

There are available for review, 264 instances of cholecystectomy, whose records include follow-up notes extending over a period of at least one year, a follow-up percentage of 85 of all cholecystectomies performed during this period. Two hundred thirty-six of these patients, or 89 per cent, have reported themselves in good health and relieved of all symptoms. In the records of the remaining 28, mention is made of one or more residual symptoms. In seven instances, these symptoms were found on investigation to be due to causes extraneous to the biliary tract and for the most part developing after the operation. These patients were entirely free of symptoms related to the gallbladder or ducts and will be discussed as Group IV. In five patients, notes made soon after operation indicate persistence of biliary symptoms, but later the patients in this group (Group III) obtained complete relief. There are left 16 patients with residual trouble of one form or another, definitely attributable to the biliary system, or attributed to this system correctly or incorrectly at the time operation was determined upon. To put the matter in another way, this analysis shows that cholecystectomy gave ultimate relief to 94 per cent.

The 16 unrelieved patients may be subdivided into two groups. Group I are those in whom no significant biliary lesion was found at operation. The preoperative diagnosis was, therefore, incorrect. Group II consists of those who, at operation, had definite lesions of the gallbladder or its ducts but whose symptoms persisted despite the removal of the gallbladder. In most instances, these patients gave atypical histories of gallbladder disease or re-

ported symptoms additional to those which could be related to the biliary tract. The diagnosis of gallbladder disease in these instances, therefore, only partially explained the patients' symptomatology, and this diagnosis can be described as incomplete. A careful analysis of these cases of an incorrect or incomplete preoperative diagnosis brings to light some interesting features.

Although the ratio of males to females in the entire series of biliary operations reported by Eliason and Erb<sup>2</sup> is approximately one in six, there was only one male in this group of 16 poor results. This emphasizes the difficulty of differential diagnosis of abdominal conditions in women. It also seems noteworthy that prior to their cholecystectomy six, or 40 per cent, of the women had had a previous pelvic operation with removal of one or both tubes and ovaries. In reviewing these records, it seems probable that the symptoms of artificial menopause complicated and confused the diagnosis of gallbladder disease.

In dealing with conditions in which the history given by the patient plays a major rôle in diagnosis, a clear understanding between the patient and the historian is of paramount importance. Frequently, errors are traceable to the fact that the patient does not comprehend our questions or else we do not understand his replies. The historian may ask leading questions and a frightened patient obligingly supplies false information. The intelligence quotient of the patient may make accurate history taking impossible or language difficulties may exist, in which case an interpreter may further complicate the situation. We have no means of assessing the part played by the first two factors in our own diagnostic errors, but it was not surprising to find that in five instances the history states that "the patient understands and speaks English very poorly." No doubt, similar but unrecorded misunderstandings arose in other cases. Often, in patients whose histories are unreliable or atypical, laboratory data have had too great an influence upon the diagnosis. For example, cholecystography is reliably accurate in determining the function of the gallbladder at the moment, so that, barring technical errors in the administration of the dye, a roentgenographic report of nonfunctioning gallbladder means exactly that. Yet that is far from implying that the impaired function of this single organ necessarily accounts for all the symptoms suffered by the individual. Every pathologist can testify that many of us live and die peacefully ignorant of the fact that our stone-laden gallbladders have neither concentrated nor emptied for years.

*Incorrect Diagnoses*—Group I. There were eight patients in whom an incorrect diagnosis of gallbladder disease was made preoperatively. Each had had adequate preoperative studies, many being investigated exhaustively on the medical service before they were transferred for surgery. In a fair number, an honest doubt as to the diagnosis was expressed at the completion of study. Nevertheless, they were operated upon with the suspicion of gallbladder disease, and cholecystectomy performed, although the surgeon could not identify gross evidence of biliary disease. Hence, they must be classed as diagnostic errors. In most instances the actual cause of the symptoms was disclosed at operation. In some, it was not evident at this time but was

made manifest or inferred from later developments. It is obvious that this small group does not include all the cases in which we committed errors of diagnosis in gallbladder disease, but only those in which cholecystectomy was performed and the results were unsatisfactory. There were other cases, of course, in which the operator left the gallbladder intact or simply drained it when his preoperative diagnosis was found to be in error. In the light of later developments, the sources of error often stood out strikingly and symptoms which were passed over as unimportant took on a new significance. Such was the case in a patient (Case 1) who two years after cholecystectomy was found to have a huge carcinoma of the greater curvature of the stomach. The same is true of the one diagnosed pylorospasm (Case 2). At operation both stomach and duodenum were inspected and palpated but the negative roentgenologic studies of the gastro-intestinal tract doubtless deterred the surgeon from opening the stomach. Had this been done, an ulcer on the posterior wall might have been found. A case designated as perihepatitis (Case 3) is of more than usual interest. Fitz-Hugh<sup>3</sup> has described this condition, and attributed it to gonococcal infection originating in the pelvic organs. In this patient there was an acute serositis of the hepatic capsule and adjoining parietal peritoneum, with filmy adhesions. The clinical picture was that of acute cholecystitis. Another case, studied on the Neurologic Service, presented many symptoms which could be interpreted as fairly typical of gallbladder disease. At that time we were unfamiliar with the clinical picture of hyperinsulinism resulting from a pancreatic adenoma. It is interesting to speculate upon whether the "fits," for which she was admitted to the hospital, were due to this cause. The question cannot be answered since no blood sugar determinations were made and the patient cannot be traced. A functional digestive disorder seems a reasonable diagnosis in this patient as well as in one other in the series (Cases 4 and 5). Three diagnoses were corrected to adhesions, in two instances postoperative and in the third congenital (Cases 6, 7 and 8). The diagnosis of gallbladder disease, in each case, was made with reservations because of the history. None benefited from cholecystectomy, and improvement was hardly to be expected, inasmuch as the principal lesion lay outside the gallbladder. It will be noted that several of these patients had stones, pericholecystic adhesions or other evidence of cholecystic disease, so to that extent the diagnosis was correct. Brief abstracts of the records of these eight cases follow.

## BRIEF ABSTRACTS OF EIGHT CASES WITH INCORRECT PREOPERATIVE DIAGNOSES

*Group I**Cases with No Significant Gallbladder Lesions***Case 1—Gastric Carcinoma** Female, age 54

*History*—Nausea, vomiting and gaseous distention—four years. Hunger pains two to three hours after meals. Two attacks of right upper quadrant pain with some jaundice, none of this pain recently. Weight loss of 50 pounds in year. Cholecystogram—nonfunctioning gallbladder.

*Operation*—Single stone at ampulla. Chronic thickening of gallbladder wall. No stones felt in common duct. No note about stomach or duodenum.

*Result*—Continued pain, gaseous distention and occasional diarrhea. Lost more weight. After 21 months, a large carcinoma of greater curvature of stomach was found during course of pelvic operation. (Note early symptoms overlooked.)

*Case 2—Pylorospasm* Female, age 32

*History*—Recurrent epigastric pain—five years—food relief. Nausea. Flatulence. Loss of 20 pounds in five months. Anorexia. Gastro-intestinal series negative.

*Operation*—Hypertrophy and spasm at pylorus, no ulcer found. Adhesions around gallbladder. No stones.

*Result*—Burning in epigastrium returned four months after operation. After two years, advised admission to Medical Ward with diagnosis of peptic ulcer, but patient went elsewhere.

*Case 3—Perihepatitis* Female, age 26

*History*—Pain in right upper quadrant, six days—worse on deep breathing. Nausea and vomiting. Local tenderness and rigidity.

*Operation*—Perihepatitis—acute, possible gonococcal origin (previous operation for tubal disease). No biliary lesion.

*Result*—Two years—persistent gaseous indigestion.

*Case 4—Functional Nervosis* Female, age 45

*History*—Admitted to Neurologic Service because of so-called "fits." Multiple complaints, including gaseous dyspepsia and jaundice, from which history of gallbladder dyspepsia could be inferred. During "fit," local signs suggested cholecystitis. Cholecystogram—nonfunctioning gallbladder. Medical consultant doubtful about organic disease.

*Operation*—Fatty infiltration of gallbladder, and enlarged lymph node near cystic duct. No stones.

*Result*—Improved, but still has epigastric distress. (Question of pancreatic adenoma.)

*Case 5—Functional Nervosis* Female, age 38

*History*—Nausea, vomiting and diarrhea for 20 years. Studied, Discharged. Returned two years later, with story of pain in right upper quadrant and reported transient jaundice. Gastro-intestinal series negative.

*Operation*—Possible kinking of cystic duct, and slight thickening of gallbladder wall. No stones.

*Result*—During following two years two readmissions for vomiting, which was never verified.

*Case 6—Postoperative Adhesions* Female, age 44

*History*—1905, indigestion began following pregnancy. 1915, pelvic operation. 1925, cholecystectomy performed in another hospital for colic and jaundice. Three later admissions to same hospital—diagnosed adhesions. 1932, admitted with history of pain in scapular region, nausea, chills but no jaundice. Roentgenogram indicated adhesions. Operated upon, because of suspicion of common duct stone.

*Operation*—Extensive adhesions, some of which thought to cause kinking of common duct. Latter explored. No stones or obstruction.

*Result*—During next two years, recurrent attacks of pain with nausea.

*Case 7—Adhesions—Duodenal Ileus* Female, age 46

*History*—Typical history of colic, indigestion but no jaundice—two years. Vomiting with relief.

*Operation*—Adhesive bands making traction on cystic duct, and involving also duodenum and colon. No stones.

*Result*—Relief for one month. Symptoms returned. Gastro-intestinal series showed duodenal stasis. Reoperated upon, and duodenojejunostomy performed. Relieved for 15 months, when pain returned. Reoperated upon, and adhesions freed. Four months later, same incapacitating pain.

*Case 8—Postoperative Adhesions* Female, age 32

*History*—Nausea, belching and constipation since childhood. Appendectomy, and subsequent operation for intestinal obstruction due to adhesions. Recent attacks of severe

right upper quadrant pain, referred to shoulder Cholecystogram—normal function Gastro-intestinal series—irregularity in pyloric region suggesting prolapse of mucosa

*Operation*—Extensive adhesions Stomach and duodenum normal Cholesterosis of gallbladder

*Result*—Continued upper abdominal pain for two years, with eventual reoperation elsewhere, for intestinal obstruction

*Incomplete Diagnoses*—Group II A second group of eight patients consisted of those in whom, as has been stated, the diagnosis was partially correct, in that a definite cholecystic lesion was found at operation Correction of the local condition by cholecystectomy, however, failed to relieve all the symptoms, and the latter may be attributed to the presence of "silent stone," the existence of which was disclosed only by roentgenologic examination It is significant that in each case the biliary symptomatology was complicated by other complaints Usually, thorough investigation, or the developments of time, threw light upon the real sources of distress in these patients In three instances, we remain uncertain concerning the cause of their complaints It may be suspected at first glance that this group contained patients in whom common duct stones were overlooked at the time of cholecystectomy This has been emphasized by numerous authors, including Cattell,<sup>1</sup> in their analyses of cholecystectomy failures None of these cases of ours had jaundice, chills, fever or other manifestations of common duct obstruction So far as we are able to ascertain, none of these unsatisfactory results were due to undiscovered stones in the ducts, although we have operated upon such patients who have had a cholecystectomy elsewhere, and some of ours may have gone to other surgeons rather than return to our Follow-Up Clinic The common duct was explored in 18 per cent of the total number of operations for inflammatory disease of the gallbladder In about one-third of these, the gallbladder was emptied and drained instead of being removed This was sometimes done deliberately in cases in which the operator felt that possible undiscovered stones remained in the ducts The presence of the gallbladder provides a valuable anatomic landmark in the event of secondary explorations of the ducts Common duct stricture due to operative trauma occurred in one case not included in this discussion, owing to the fact that following early reoperation, a perfect functional result was secured Although seven of the eight cases in this group had cholelithiasis, this does not invalidate the accepted contention that the best results of cholecystectomy occur in calculous rather than in noncalculous gallbladders It merely emphasizes the fact that the presence of stones in the gallbladder or even in the ducts does not of necessity mean that the patient will have symptoms therefrom Actually, only 15 per cent of the cholecystectomies included in this series were performed for chronic, noncalculous cholecystitis Cholecystostomy was frequently performed in the noncalculous cases, when the operator was doubtful whether the gross signs justified cholecystectomy Attention is called to the atypical history in each case in the appended abstracts (Group II) Two patients suspected of peptic ulcer are perhaps noteworthy In one (Case 2), this was the preoperative diagnosis At operation, the surgeon, after search-

ing in vain for ulcer, removed the gallbladder. The residual symptoms suggest that symptoms were due to the phrenospasm and duodenal stasis apparent on roentgenologic examination. In the second (Case 5), ulcer was suspected from the roentgenologic evidence of deformity of the duodenal cap. Pericholecystic adhesions found at operation seemed to account adequately for this defect. Unfortunately, no note was made concerning inspection or palpation of the duodenum, so we are left uncertain as to the correct explanation of the case. The recorded postoperative complaints, it must be admitted, were not typical of ulcer in this case.

BRIEF ABSTRACTS OF EIGHT CASES WITH INCOMPLETE DIAGNOSES

Group II

*Cases With Definite Lesions of the Gallbladder, in Which Symptoms Persisted*

**Case 1**—Female, age 32

*History*—Atypical history of pain in left hypochondrium, eructations, fulness after meals, headache and constipation.

*Operation*—Single stone. Adhesions about appendix, removed with gallbladder.

*Result*—Same symptoms as before operation. Colon responsible?

**Case 2**—Female, age 54

*History*—Burning epigastric pain—one year—usually a few hours after eating, and always relieved by soda. Gastro-intestinal series showed phrenospasm and duodenal diverticulum, with stasis in second portion. Tentative diagnosis: Duodenal ulcer.

*Operation*—Inspection and palpation of stomach and duodenum revealed no ulcer. Gallbladder wall thickened, and stone impacted in cystic duct.

*Result*—During following two and one-half years, continuous gaseous indigestion—sour regurgitations, distress after fatty foods.

*Conclusion*—No relief from operation due to concomitant duodenal disorder.

**Case 3**—Female, age 48

*History*—Bilateral salpingo-oophorectomy for a Sampson's cyst, eight years before. Indigestion with severe right upper quadrant pain—two years. Epigastric hernia found, relief secured from belt. Recently, constant discomfort in upper abdomen relieved by soda. Some tenderness over gallbladder. Operation undertaken as diagnostic procedure. Diagnosis: Gallbladder disease or colonic adhesions. Marked cancerphobia.

*Operation*—Gallbladder gray and thickened. Common duct, not dilated.

*Result*—During next year, continued distress—complete investigation. Diagnosis: Anxiety neurosis and endocrine dysfunction.

**Case 4**—Female, age 49

*History*—Typical, with many additional symptoms, including hunger pains relieved by food and generalized neuralgias.

*Operation*—Single stone. Adhesions about gallbladder. Cirrhosis of liver.

*Result*—None of previous colic, but all other symptoms persistent over three-year period. Hepatic disease?

**Case 5**—Male, age 29

*History*—Typical indigestion, without colic—three years. Cholecystogram—nonfunctioning gallbladder. Gastro-intestinal series showed duodenal defect, probably due to adhesions but possibly an ulcer.

*Operation*—Adhesions to gallbladder. Stones. No note about duodenum.

*Result*—Not relieved after 18 months. Symptoms may be due to ulcer in addition to biliary lesion.

**Case 6**—Female, age 53

*History*—Atypical. Pain chiefly in left upper quadrant and referred to scapulae—indi-

gestion Linguistic difficulties Gallbladder palpable Cholecystogram—nonfunctioning gallbladder Laboratory evidence of slight icterus

*Operation*—Many stones

*Result*—Two years, complains of same symptoms but especially pain in left side  
Etiology unknown Silent stones

**Case 7**—Female, age 30

*History*—Adhesions about gallbladder Stones palpated during pelvic operation  
Later had colic referred to back and shoulder, vomiting and diarrhea

*Operation*—Thickened gallbladder, with stones and adhesions One stone in cystic duct

*Result*—Symptoms, similar to those above, together with intractable constipation and backache Functional disturbance of colon?

**Case 8**—Female, age 36

*History*—Linguistic difficulties Epigastric pain—nausea—belching Questionable diagnosis Cholecystogram—no function of gallbladder Gastro-intestinal series—probably adhesions about duodenum cap Cholesterol crystals in duodenal drainage Cystoscopic examination negative

*Operation*—Many stones

*Result*—Seven months, same symptoms persist Definite postoperative cystitis Silent stones with additional obscure factors

*Delayed Relief from Operation*—Group III We have designated as Group III, five patients who had, for from six to 16 months, symptoms similar to those which preceded operation Eventually, they became well, and were considered as satisfactory results We have usually attributed this delay in relief from cholecystectomy to the fact that time is required for the ducts to dilate, so that they may assume, in a measure, the function of the absent gallbladder We had thought this delay was particularly apt to occur in young patients, or in those with biliary duct obstruction of brief duration and have made a point of warning such patients that they must not expect immediate cessation of all indigestion This particular group does not bear out these particular impressions

#### BRIEF ABSTRACTS OF FOUR CASES WITH DELAYED RELIEF FOLLOWING OPERATION

##### *Group III*

##### *Cases with Delayed Relief Following Operation*

**Case 1**—Age 25 Typical history—six years Aerophagia No calculi Well, after nine months

**Case 2**—Age 54 Typical history with colic—three years—and jaundice Stones and adhesions Persistent indigestion, first 16 months

**Case 3**—Age 38 Atypical history—several years with pain and distention Stones and adhesions Several attacks of severe pain, first year None thereafter

**Case 4**—Age 53 Typical history—seven years Stones and adhesions Distress after eating, first six months Well thereafter

*Extraneous Complications*—Group IV Our follow-up records were confused, at first inspection, by a number of patients who appeared to have residual troubles after operation Careful analysis revealed that their symptoms were not biliary in origin, and we have designated this group of patients as Group IV They were, in reality, relieved by the operation of all symp-

toms related to the gallbladder and then complaints, with two exceptions, arose after operation. In these two instances a second condition—hyperthyroidism and myocardial disease—was clearly recognized before operation, but cholecystectomy was considered advisable, as it might benefit the concomitant condition. Under such circumstances, we have not designated these as diagnostic errors. Appended is a list of the sources of their symptomatology.

#### *Group IV—Extraneous Conditions*

- (1) Ureteral colic—right-sided
- (2) Ulcerative colitis, with epigastric pain
- (3) Pulmonary and intestinal tuberculosis, with dyspepsia
- (4) Tabes dorsalis, with epigastric pain
- (5) Subacromial bursitis—right shoulder pain
- (6) Hyperthyroidism, recognized before gallbladder operation, and not relieved by thyroidectomy
- (7) Myocardial disease, with fibrillation present before operation and persisting

#### CONCLUSIONS

A study of a series of 264 cases, in which cholecystectomy was performed, with a preoperative diagnosis of cholecystitis, shows that only 6 per cent were not relieved of the symptoms for which operation was performed. In a small number this relief was delayed, and in others extraneous factors developed after operation which were attributed, incorrectly by the patient, to the gallbladder. The 6 per cent who continued with many of the same symptoms after removal of their gallbladders fall into two equal groups. In one, no gross evidence of gallbladder disease was evident at the time of operation, and cholecystectomy could not be expected to afford relief. In the other, the surgeon found a diseased gallbladder, and usually gallstones, yet the patient was not helped by cholecystectomy. In this latter group, the chief source of the patient's complaints was extrabiliary and the finding of a biliary lesion purely incidental. A certain number of these diagnostic errors were inevitable, despite thorough preoperative study of the cases. In others, the errors might have been avoided by attaching due significance to symptoms which were regarded simply as atypical, by more careful attention to the patients' own description of their symptoms, and by a recognition of the fact that, even when gallstones are actually demonstrated, it may not be fair to attribute thereto all the patients' digestive symptoms, since many gallstones are "silent" ones.

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# PROTHROMBIN DEFICIENCY AND THE EFFECTS OF VITAMIN K IN OBSTRUCTIVE JAUNDICE AND BILIARY FISTULA

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WHEN Dam,<sup>1</sup> in 1935, showed that the lack of a fat-soluble substance which he called vitamin K (koagulations vitamin) in the diet of chicks led to fatal bleeding, he opened a new approach to the study of pathologic bleeding. Investigation of a hemorrhagic disease of cattle resulting from eating spoiled sweet clover had led to demonstration of low plasma prothrombin as the etiologic factor, presumably due to toxic effect on the liver.<sup>2</sup> Improvements in methods of determining plasma prothrombin<sup>3, 4</sup> were followed by observation of low plasma prothrombin in animals with experimental liver poisoning and biliary obstruction, in chicks with hemorrhagic disease from vitamin K deficiency, and in patients with obstructive jaundice.<sup>5, 6, 7</sup>

Another link in the chain was supplied by the experimental proof that fat-soluble vitamins are not absorbed from the intestine in the absence of bile salts.<sup>8</sup> Practical application of these facts has led to successful treatment of prothrombin deficiency in patients with liver disease by means of extracts containing vitamin K.<sup>9, 10</sup> Considerable progress has been made in the purification of vitamin K, though a preparation suitable for parenteral use is not yet available. Much study has been given to developing better methods of assaying the vitamin K content of various animal and vegetable fats, but a method based on the protective or curative effect on chicks must still be used.<sup>11</sup>

Data included in the present communication were obtained in the study and treatment of patients with obstructive jaundice or biliary fistula on the Surgical Services of the Massachusetts General Hospital during the past year. Although the work is now in progress, the results to date are so striking that it is felt a preliminary report is indicated.

*Methods Employed*—Plasma prothrombin was determined by the method of Warner, Brinkhous and Smith,<sup>5</sup> with modifications. Instead of using serial dilution technic, standardized normal control plasma was titrated in exactly the same way as the unknown, both being done in triplicate. The incubation period of the mixture before adding fibrinogen was kept constant and brief. Since the final coagulation time is taken as inversely proportional to the prothrombin concentration, there results the formula,  $\frac{TC}{TX} \times \frac{DC}{DX} = \text{percent-}$

age of normal plasma prothrombin is unknown, where TC = clotting time of control, TX = clotting time of unknown, DC = dilution factor of control and DX = dilution factor of unknown. Fresh plasma is taken from the control for each set of titrations. A group of six laboratory workers were used as controls, and little difference among them or variation from time to time was observed, so long as titration temperature was kept constant. Each new lot of reagents, however, must be standardized.

In every instance the clotting time of recalcified plasma with addition of excess of thromboplastin (beef lung extract) was determined. As a rule this gave results in relation to the normal control similar to those obtained by the method of Warner, Brinkhous and Smith. Occasionally, however, particularly in abnormal plasma, there was wide discrepancy. The results obtained with the method of recalcification of oxalated plasma to which thromboplastin has been added are not reported here.

Fibrinogen was determined in duplicate on the oxalated plasma by the method of Cullen and Van Slyke,<sup>12</sup> the clot obtained from 1 cc of plasma being subjected to microdigestion and nesslerization. In several instances dilute thrombin solution was used to precipitate the fibrinogen and the results checked closely with those obtained by using calcium chloride. This was done to exclude the possibility of incomplete conversion of fibrinogen to fibrin in the presence of prothrombin deficiency.

Plasma bilirubin was measured as follows. Two cubic centimeters of plasma were combined with 1 cc of the diazo reagent and allowed to stand ten minutes. Then 2 cc saturated ammonium sulphate plus 10 cc 95 per cent alcohol were added. The mixture was centrifuged, and the supernatant fluid was read against the cobaltous sulphate standard prepared according to McNee and Keefer.<sup>13</sup>

Various liver function tests were performed repeatedly on these patients, including the bromphalein and hippuric acid tests. These data, however, will not be discussed here.

The vitamin K extract used in this work was prepared from fresh spinach according to the method of Dam.<sup>14</sup> The extraction was continued through the acetone and petroleum ether refluxings, and from 50 kg of spinach 30 Gm of tarry liquid were obtained. The extract was thoroughly mixed with sodium taurocholate and sodium glycocholate (Merck) in the proportion of 1.0 Gm of extract to 4.5 Gm of each bile salt preparation, and the mixture was put up in capsules containing 0.2 Gm each. The mixture was kept in a cold box at  $-35^{\circ}\text{C}$ , used also for preserving the solutions of fibrinogen, thrombin and thromboplastin.

Usually determination of plasma prothrombin was made repeatedly before and after operation, and vitamin K-cholic acid mixture was given orally as needed. In two cases, patients T. P. H. and M. Y., the mixture was given through a jejunostomy. One patient, M. Y., was seen only after operation, when massive bleeding had set in and six transfusions had been ineffective in controlling it.

*Results Obtained*—In Table I are shown data from 13 patients, 12 of whom were suffering from obstructive jaundice and varying degrees of liver damage, while one, M Y, had a postoperative external biliary fistula. The amount of vitamin K-cholic acid mixture taken and the duration of treatment are shown, together with plasma concentrations of prothrombin and bilirubin. The average increase in plasma prothrombin under vitamin K therapy was 32.8 per cent.

TABLE I

PREOPERATIVE RESPONSE OF PLASMA PROTHROMBIN LEVEL TO VITAMIN K-CHOLIC ACID MIXTURE\*

Patient	Age	Diagnosis	Jaundice, Dura- tion, Weeks	Treat- ment, Duration, Days	Vitamin K Bile Salts, Total Gm	Plasma Pro- thrombin Per Cent	Plasma Bilirubin Mg Per Cent
L H S	33	Common duct stone	14	4	3.2	49.8 86.8	10.1 10.1
J B	47	Carcinoma of pancreas	3	5	4.0	71.4 86.6	19.2 24.2
H C K	32	Common duct stricture	4	4	3.2	71.1 95.7	11.6 11.0
C J	59	Common duct stone	2	4	7.8	59.2 102.0	40.0 41.7
M A C	41	Common duct stone	4	5	7.4	42.4 96.4	9.9 12.3
D F W	39	Common duct stone	2	2	5.8	35.7 83.3	15.0 19.2
P W	58	Carcinoma of pancreas	6	3	9.0	28.9 96.1	19.6 19.6
J R B	53	Carcinoma of pancreas	1.5	6	24.8	83.2 100.0	12.5 26.6
T P H	66	Carcinoma of pancreas	6	2	5.7	28.0 56.7	43.5 38.4
M L K	61	Common duct stone	12	5	6.0	70.7 100.0	13.1 16.7
J F	46	Common duct stone	1.5	4	3.2	75.6 87.2	6.0 1.0
R M	75	Carcinoma of pancreas	7	1	0.8	40.5 61.1	16.3 16.5
M Y	34	Biliary fistula		6	7.2	37.5 68.9	1.0 1.0

\* Increase from initial average of 53.4 per cent to 86.2 per cent after treatment, average days of treatment = 3.9, average dose = 6.8 Gm.

In Table II are shown plasma prothrombin concentrations in five patients suffering from massive postoperative hemorrhage. Data from three of these patients are shown graphically in Charts 1, 2 and 3. Patients M Y, J R B and H C K were given vitamin K-cholic acid mixture immediately and the bleeding ceased with a dramatic rise in plasma prothrombin. Patient T P H developed severe diarrhea when the mixture was given through a

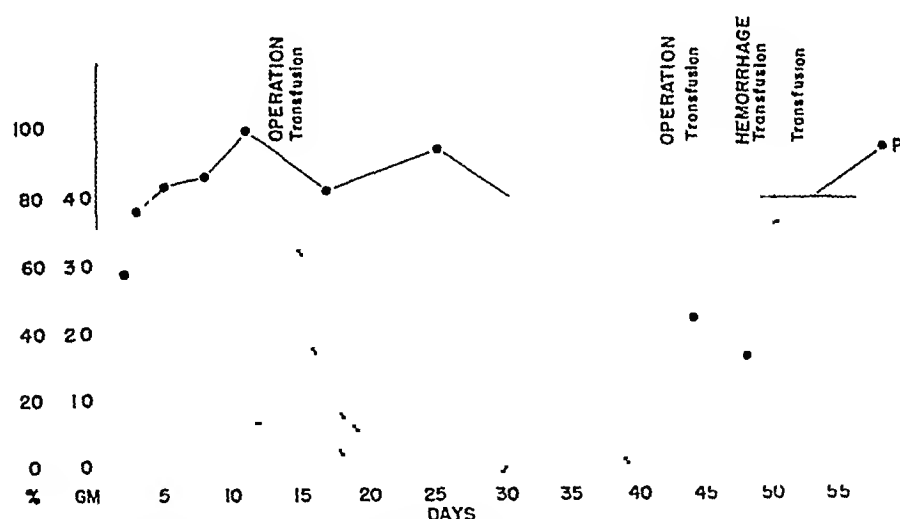
# PROTHROMBIN DEFICIENCY

TABLE II  
DATA IN CASES OF POSTOPERATIVE BLEEDING\*

Patient	Operation	Post-operative Day	Bleeding		Site
			Plasma Prothrombin Per Cent		
T P H	Cholecystostomy	4th	43 7		Urinary and biliary tracts, retroperitoneal tissues
J R B	Cholecystogastrostomy	7th	32 3		Stomach, gallbladder
M Y	Repair of common duct	6th	37 5		Wound, gastro-intestinal tract
M L K	Exploratory celiotomy Biopsy of liver	8th	38 6		Wound, uterus
H C K	Choledochostomy	16th	38 9		Wound, gastro-intestinal tract

\* M L K and M Y had no vitamin K after operation, J R B and H C K had refused further administration of vitamin K, T P H had developed severe diarrhea, M Y had had transfusion of 3,000 cc of blood during previous 48 hours

jejunostomy, and the bleeding was uncontrolled. The prothrombin level remained low until the patient succumbed to anuria and liver failure. Patient M L K received no vitamin K-cholic acid mixture after operation owing to the onset of uremic stupor and vomiting. Cirrhosis of the liver, ascites, and



J R B Plasma Prothrombin in Obstructive Jaundice

CHART 1—Patient J R B Showing plasma prothrombin in relation to varying vitamin K cholic acid intake and operation. Refusal of patient to take mixture after second operation, leading to fall in prothrombin and massive hemorrhage. First operation was cholecystostomy, the second cholecystogastrostomy, P represents the plasma prothrombin in per cent of normal, the dosage of vitamin K cholic acid mixture, in grams, is shown in the checkered columns

anuria made the outlook seem hopeless, and jejunostomy for feeding vitamin K was not performed.

*Discussion*—The frequency with which plasma prothrombin is reduced in obstructive jaundice is striking. During the course of this study only one case has been seen in which obstruction to bile flow for over a week

has not been associated with plasma prothrombin levels of less than 84 per cent. In this case the patient's appetite had remained remarkably good and the biliary obstruction was incomplete. In the preoperative group the response

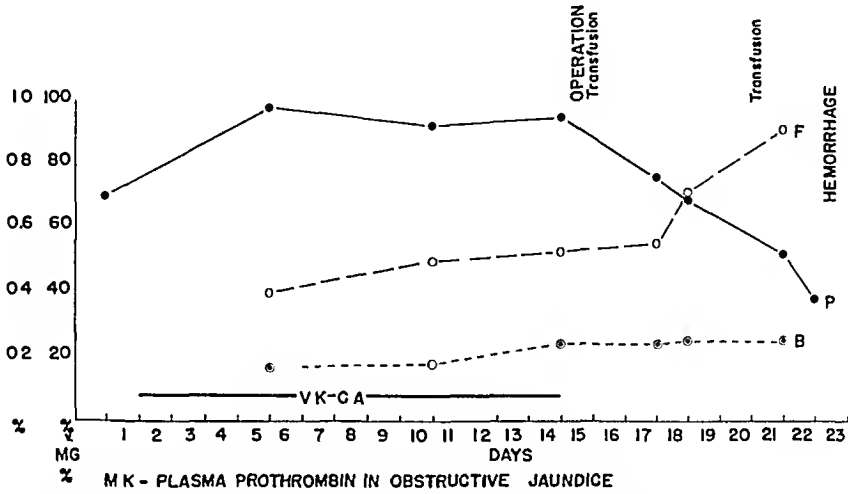


CHART 2—Patient M L K Showing plasma prothrombin and fibrinogen in relation to operation and vitamin K cholic acid intake. Preoperative response to the medication is well shown with progressive postoperative fall in prothrombin leading to gross hemorrhage no vitamin K being taken after operation. The failure of blood transfusion to prevent hemorrhage is obvious. P represents the plasma prothrombin in per cent of normal, F represents the plasma fibrinogen percentage, B represents the plasma bilirubin in milligrams per cent.

to vitamin K-cholic acid has been invariable. It seems to be true, however, that the more severe the liver damage the less marked is the prothrombin recovery. This can be illustrated by data in Table I. Patient T P H

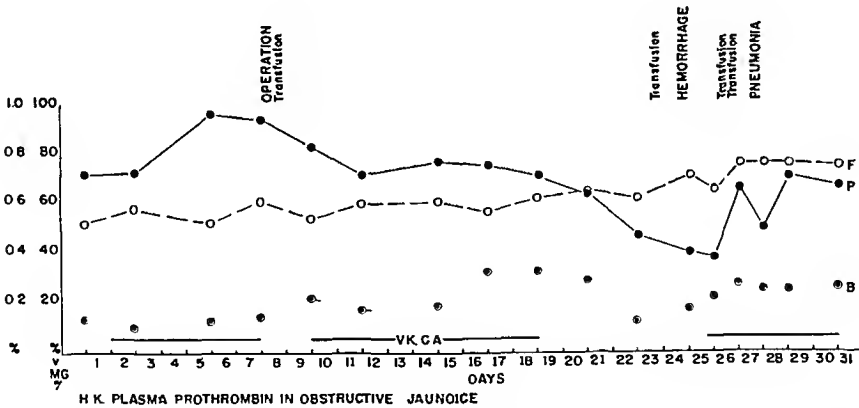


CHART 3.—Patient H C K Showing the effect of operation, vitamin K cholic acid mixture and pneumonia on the plasma prothrombin and the fibrinogen. Preoperative response of prothrombin well shown. Note the effect of withdrawal of vitamin K cholic acid in the presence of persistent jaundice, resulting in massive hemorrhage with recovery on resumption of vitamin K mixture. Ineffectiveness of transfusion brought out. P represents the plasma prothrombin in per cent of normal. F represents the plasma fibrinogen percentage, B represents the plasma bilirubin in milligrams per cent.

entered the hospital in a moribund state with carcinoma of the pancreas, complete biliary obstruction, liver failure, oliguria, ascites and peripheral edema. The prothrombin response to vitamin K-cholic acid therapy in two days of treatment was only moderate.

Little if any correlation is discernible between the degree of depression of plasma prothrombin and the plasma bilirubin level. This is not surprising since the excretory function of the liver is only one of the factors concerned in the maintenance of plasma prothrombin. Also, even when bilirubin is being excreted, bile deficient in cholic acid and hence less effective in promoting absorption of vitamin K may be formed by the damaged liver.

A drop of 20 to 40 per cent in plasma prothrombin concentration immediately after operation is to be expected, dependent perhaps on such factors as blood loss and dilution of plasma, clotting, and depression of liver function by anoxemia and anesthesia. The fall is transitory, however, if vitamin K-cholic acid feeding is resumed at once. These points are illustrated in Chart 4.

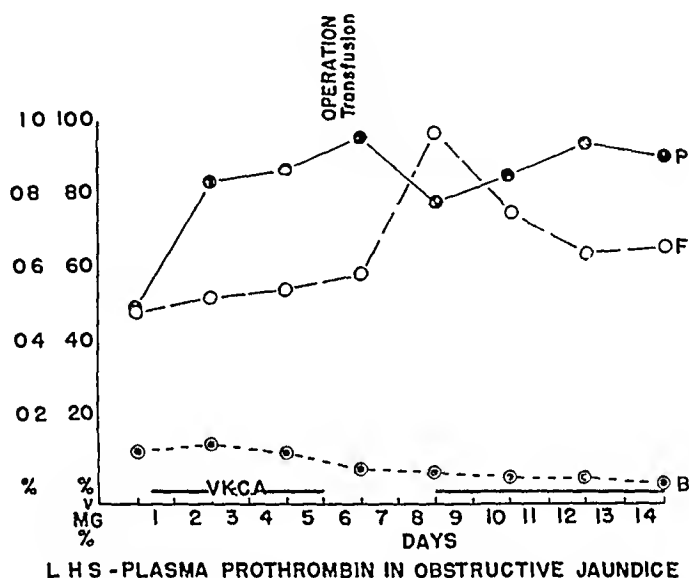


CHART 4.—Patient L. H. S. Showing the plasma prothrombin in relation to the intake of vitamin K-cholic acid mixture and operation. Postoperative drop with prompt recovery on taking mixture is shown. P represents the plasma prothrombin in per cent of normal, F represents the plasma fibrinogen percentage, B represents the plasma bilirubin in milligrams per cent.

It is apparent that the plasma prothrombin level is quickly responsive to change in metabolic conditions, suggesting the absence of prothrombin reserves in these patients. A safe preoperative plasma prothrombin level, preferably above 75 per cent, is highly desirable. Since the prothrombin level may change quickly, the need for frequent determinations in the early postoperative course, as pointed out by Snell, Butt and Osterberg,<sup>15</sup> is obvious.

In considering the five cases of postoperative hemorrhage, several points stand out. Two patients, J. R. B. and H. C. K., created an interesting experiment by refusing to take the vitamin K-cholic acid capsules after operation on grounds that they caused epigastric distress. In both cases, as shown in Charts 1 and 3, a steady drop in plasma prothrombin with subsequent massive hemorrhage resulted. Thereafter, the patients cooperated in taking the mixture and rapid restoration of plasma prothrombin and cessation of bleeding followed. The biliary obstruction in patient H. C. K. continued

only partially relieved after operation in consequence of cholangitis, and bleeding set in as late as the sixteenth postoperative day (Chart 3). Undoubtedly the vitamin K, taken for eight days after operation, postponed the bleeding, for, as a rule, bleeding from prothrombin-lack occurs within the first week after operation.

A question of considerable interest, which deserves study, is the influence of infection on plasma prothrombin. There is some evidence that the liver may react sensitively to extrahepatic inflammation, for example, the rise in plasma fibrinogen occurring in the course of abscess formation and in pneumonia. In this connection the data shown in Chart 4 are pertinent. After the plasma prothrombin began to respond to vitamin K-cholic acid therapy following hemorrhage, a bilateral severe pneumonia suddenly set in. The plasma prothrombin level fell, whereas the plasma fibrinogen rose. In Charts 2, 3 and 4 also the lack of relationship between changes in plasma fibrinogen and prothrombin is brought out.

Blood transfusion appears to be a rather inefficient method of combating the bleeding tendency due to hypoprothrombinemia, as the effect on the recipient's plasma prothrombin is slight and transitory. A measurable increase of only 6 per cent occurred in one adult patient whose plasma prothrombin level was determined before and after transfusion of 600 cc of blood. Blood transfusion is needed to replace lost blood, but vitamin K-cholic acid therapy is indicated in order to prevent further bleeding.

### CONCLUSIONS

(1) In obstructive jaundice and biliary fistula the plasma prothrombin level may be low.

(2) Following operation upon such patients, further reduction in the plasma prothrombin may occur.

(3) Dangerous bleeding may take place with plasma prothrombin concentration of less than 50 per cent normal.

(4) No correlation can be made out between plasma fibrinogen and prothrombin concentrations.

(5) Administration of a mixture of vitamin K and bile salts, through a jejunostomy if necessary, leads to a restoration of plasma prothrombin and control of the bleeding tendency.

(6) Plasma prothrombin level depends on the functional capacity of the liver as well as absorption of vitamin K from the intestine.

The author wishes to express his gratitude to Dr H P Smith for his courteous help in the details of the prothrombin determination.

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# ACUTE HEMATOGENOUS OSTEOMYELITIS OF THE LONG BONES\*

A CLINICAL REVIEW OF 160 CASES

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IN SELECTING a topic for the Annual Oration, it seemed fitting to choose one dealing with a condition which is not only frequently encountered by both surgeon and internist and about which there exists a considerable difference of opinion as to the choice of treatment, but also one in which, regardless of the method of therapy employed, the mortality is still far greater than it should be, namely, acute hematogenous osteomyelitis

This mortality is all the more lamentable because in few other major surgical conditions should a diagnosis be made more readily, since in the vast majority of cases the patient seeks medical relief within a short time of the onset of the disease, hence, failure to obtain a satisfactory result can seldom be attributed to procrastination on the part of the patient—this factor only too often being exhibited rather by the physician who first sees the case

Aside from the question of mortality, when one considers the degree of morbidity which so frequently accompanies this condition, whether it be deformity of the involved limb or limbs, ankylosis of joints, or persistence of infection as exemplified by long delayed and residual sequestration, chronic pyogenic infection, *etc*, one can readily appreciate the importance of the early institution of that method of treatment by which these sequelae may best be avoided

That a wide difference of opinion exists as to the most satisfactory method of handling acute hematogenous osteomyelitis, is shown by the voluminous literature which has appeared on the subject, especially in recent years, after even a cursory review of which one is left in rather considerable doubt as to just what is the best method of handling this condition

In the hope that it might be possible to help, in even a very minor degree, in the solution of the clinical aspect of this problem, we have examined the records of 160 cases of acute osteomyelitis compiled from the records of the Pennsylvania, Graduate, Childrens, Presbyterian and Germantown Hospitals in Philadelphia, and the Bryn Mawr and Burlington County Hospitals †

It is not within the scope of this paper to review in detail the etiology, pathology and symptoms of acute osteomyelitis, as this information is readily

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† The author is indebted to Drs T McK Downs, Thomas J Summey, H L Farrell and Orville C King for their generous cooperation in assembling the statistics upon which this presentation is based, and to the various chiefs of the above mentioned hospitals who have permitted use of their case histories

available in any of the numerous publications on the subject, but rather in this respect, merely to briefly mention a few of the more salient factors which should be borne in mind when called upon to treat this condition

This communication is limited to a discussion of that form of acute osteomyelitis of the long bones which occurs chiefly in children and young adults, is blood borne in distribution, and is caused most frequently by some form of *Staphylococcus* or *Streptococcus* or both, and occasionally by the pneumococcus or *Bacillus typhosus*. It does not include those cases associated with compound fracture nor the more indolent types of infection, such as tuberculosis and syphilis, and that encountered in Brodie's abscess nor the sclerosing osteomyelitis of Garie

Acute hematogenous osteomyelitis may be regarded as a more or less rapidly developing osseous inflammation resulting from a blood borne infection, in which the bacteria usually lodge in that portion of the cancellous part of the metaphysis abutting upon the epiphysis. This region of bone, being richly supplied by terminal capillary loops and the blood current being slowed in this capillary bed, readily affords the organisms an opportunity to settle in this locality

In this connection, Frazer advances the theory that localization of an abscess in the bone marrow, although creating a difficult and regrettable situation as far as the local infection and suppuration are concerned, may have a salutary effect, as it may be the body's method of producing a defensive area from which the factors of immunity may be developed. He argues that a general blood borne infection may have less serious consequences if the infection becomes localized in a bone abscess

The experimental work of Lexer, to which reference is made by many writers, is also of interest in this respect, as he showed that the introduction of large numbers of bacteria into the blood stream of experimental animals produces death within 24 hours, without abscess formation. When suspensions of less virulence and weaker concentration were introduced in the same manner, the tendency was to produce abscesses in the various tissues, and the bone was most apt to be involved as the concentration and virulence of the organisms were decreased

In the human being, invasion is characterized by a tendency to rapid spread, the infection soon appearing and extending beneath the periosteum which becomes elevated from the shaft of the bone. By involving the haversian system and occluding its vessels, the infection causes an extending necrosis of the bone, and reaches the medullary cavity either by way of the haversian system, extension backward from the original focus through the cancellous part of the metaphysis, or both. Perforation of the periosteum results in soft tissue abscess with its resultant signs and symptoms

Due to the dense attachment of the periosteum to the tough epiphyseal plate, when the infection reaches the periosteum it is directed away from the epiphysis and it is usually only in the late stages of the disease that the latter, and subsequently the joint, become involved. The fact that the epiphysis re-

cerives its blood supply from a source independent of that of the shaft of the bone—branches of the articular vessels entering its surface—further tends to exclude it from involvement by an infection borne by the nutrient artery of the shaft. Concurrently with the bone invasion, there is usually a more or less profound systemic toxemia which may either rapidly prove fatal or, should it become chronic, may exhaust the patient with its complications and sequelae.

Most of the reported series of cases show a higher incidence of the disease in males—possibly due to their being more subject to local trauma and infection, such as cuts, bruises, abrasions, *etc*, nor, in this respect, should one fail to make due allowance for exposure to cold and wet. While the condition may occur at any time from birth up to the age of fusion of the epiphysis or later, its most frequent occurrence is noted between the ages of 3 and 18.

A fact not generally appreciated and well stressed by Green, is that osteomyelitis in infants under two years of age presents quite a different picture from that seen in older children, in that in the former, the infecting organism is more apt to be the *Streptococcus* rather than the *Staphylococcus*, the course being of brief rather than of long duration, the wound tends to heal rapidly rather than slowly, sequestration is infrequent rather than usual, recurrences are rare in contrast to being frequent in the older children, and the lesions usually heal completely instead of leaving a residual sclerosis of bone. The cases reported by Green and others show that the younger the infant the higher is the mortality. In the present series the age incidence was from six weeks to 50 years.

While it is true that any pus producing organism may cause osteomyelitis, yet in the vast majority of cases some form of the *Staphylococcus*, being the most frequently encountered pus producing skin organism, is most often the offending agent. In the present series, when the *Streptococcus* was encountered, it was usually associated with a focus in the pharynx, middle ear or sinuses, and a mixed infection was by no means an infrequent occurrence.

There is considerable difference of opinion as to the part that trauma exerts in localizing the lesion. The conclusion drawn by Farr would tend to belittle this as a causative factor, as he states that there is a history of injury in only about one-third of the cases, and it is often of such a trivial nature that there is no evidence of its presence at the time the patient comes under observation. He also draws attention to the fact that the part of the bone in which the infection starts is usually well protected. This latter statement, however, would not necessarily be the case in involvement of the tibia, which, in the series we are reporting, was the bone most frequently involved. Farr believes it quite likely that trauma merely focuses attention to the part involved, as is noted in other conditions—for example, cancer of the breast.

In this connection, the work of Baudet and Cahuzac is of interest. Experimenting upon rabbits, into which *Staphylococci* were injected intravenously, subperiosteally and into the metaphysis, they were unable to produce bone infection by the intravenous route even after the bone (tibia) had been traum-

atized, but infection was produced by the subperiosteal and intrametaphyseal injection, the resulting osteomyelitis, however, in no way resembling that seen in either children or adults. They further observed that when reparation of the lesion began, the blood calcium immediately decreased, as if all the resources of calcium in the body were being mobilized at the point where they were needed for the healing process. They found that the blood calcium rose gradually as the healing process progressed, and when healing was complete, it had attained normal levels. They believe that this suggests that when the blood calcium was no longer required for reparative processes in the bone it was released into the general circulation. They suggest that these findings would indicate that in osteomyelitis, estimation of the blood calcium might be of aid in determining the most opportune time for resection, which would be when the blood calcium reached its lowest level, indicating that the regenerative processes in the bone at this time are at maximum.

Earlier in this presentation, the statement was made that the diagnosis of acute osteomyelitis should not present any particular difficulty, providing the possibility of its occurrence be constantly kept in mind. While this statement holds true in the vast majority of cases, an exception may be noted in the case of infants when, as cited by Fair, the patient cannot be of much assistance in aiding the examiner to localize the site of the lesion—for example, those instances in which the onset of local edema is rapid, and the limb, when first seen, presents a swelling of the entire extremity, originating from a single focus in the bone, this occurring even in spite of the periosteum not being perforated. Under such circumstances, it is not unusual to find the swelling and tenderness, although maximal at the suspected site of the lesion, yet not sufficiently circumscribed to accurately define the area involved.

While it is also true that in most instances the signs and symptoms of acute hematogenous osteomyelitis are rather typical, yet it is in those cases presenting atypical features that one is apt to make a diagnostic error unless the condition is suspected and sought for. Among the more frequently encountered diagnostic pitfalls, perhaps acute rheumatic fever and local cellulitis head the list, and in infants one should not fail to consider joint sepsis, scurvy and occasionally hemarthrosis.

As an aid in the differential diagnosis between local cellulitis and acute osteomyelitis, we have found that the old observation of the response to continuous digital pressure over the suspected area has frequently been of considerable assistance. Should the condition be a simple cellulitis without bony involvement, the maximum discomfort of the patient is experienced when the digital pressure is first applied, and while further deep pressure causes some discomfort, it is not marked. Should the condition be osteomyelitis, the reverse is true, namely, while the initial pressure may be somewhat painful, its continuation causes an increase of pain out of proportion to the force applied. This simple expedient has been of value in cases in which, for instance, the patient has an infected lesion of the foot and one wishes to determine whether

the inflammatory reaction over the tibial area draining this region is a simple cellulitis or an acute osteomyelitis

It is well to bear in mind the fact, as stated by Homans and others, that the site in which symptoms first appear is not necessarily that in which the disease will develop. Thus, the child may have complained of pain in the region of one or more joints before developing the acute localizing lesion, these preliminary manifestations tending to confuse the picture with that of acute rheumatic fever. While it is true that acute osteomyelitis occurs most frequently in the long bones, one should bear in mind the possibility of its developing in the flat ones as well, notably the scapula and pelvis where, in the latter, it may simulate hip disease. When the condition appears in the skull it is most apt to follow an infected injury and may involve either the outer, or both tables of bone.

One may briefly summarize the question of diagnosis by stating that failure in this respect may most frequently be attributed to the fact that the condition is unsuspected.

The author is not in accord with the statement by Cutting, that "if the diagnosis is made sufficiently early and the proper treatment is then instituted, the mortality in osteomyelitis should be nil." Cutting's conclusion may be true in those instances in which a single localized focus is the only lesion, but we do not believe it can be maintained where this focus is an incidental local manifestation of an overwhelming blood stream infection. In this respect, our experience has been more in accord with that of Wilensky, who states that "every case of osteomyelitis is basically composed of two components—a general bacterial infection, be it sepsis, septicemia or bacteremia, and a local lesion in the bone tissue."

We also concur with the latter's opinion that, in the treatment of the condition in the early stages, the most important item is the general infection, and that "the ultimate outcome—death or recovery—is dependent on this above mentioned factor, and the mortality statistics of acute hematogenous osteomyelitis in its early stages reflects accurately the mortality of a general bacterial infection. When divorced from the general bacterial infection, and in the absence of any fatal complications or associated lesions, the mortality of the osseous lesion is nil." In conjunction with the above statement, one should bear in mind the possibility of converting a local lesion into an infection of the blood stream by inopportune or misdirected operative efforts.

In discussing treatment, about the only, even partial, accord one can find among various authors is as regards prophylaxis in the elimination of foci of infection throughout the body, and the avoidance of those factors such as trauma, strain, chilling, *etc*, which may be classed as physiologic attributes. The widest diversity of opinion exists as to the time and character of treatment of the local lesion, ranging from what might be classed as ultra-conservatism—purely supportive treatment with the exclusion of surgical procedures—to radical drainage, as exemplified by extensive guttering of

the involved area, or even resection of the shaft from one epiphysis to the other.

Thus, to cite but a few of the many diversified opinions in this respect, Kulowski advocates operating just as soon as the diagnosis is made, regardless of whether the condition is acute, chronic, or presents any other unusual phases of the disease. His main argument centers on the fact that pyogenic osteomyelitis is essentially a most devastating disease, which must be combated by bold, aggressive, radical operative measures. He believes that there is no proof that direct drainage of the bone in the acute stage increases the death rate, and is convinced that the vast majority of cases are undertreated. As one becomes more and more familiar with the disease, in his opinion, one is the more ready to adopt the most radical measures to attain a cure. In 92 cases of osteomyelitis of the femur, he reports a mortality of 3 per cent, and there was no mortality among 80 cases of involvement of the tibia—truly a remarkable record, which was unsurpassed by any other statistics we could find.

In a collected review of the subject, Cutting states that the operative treatment of the condition must always be considered an emergency procedure in which minutes count, and a delay of hours may mean the difference between life and death. He further is of the opinion that an operation performed at the earliest possible moment in these cases, even if performed by unskilled hands, is undoubtedly to be preferred to any considerable delay, provided the operative procedure is rational. Other things being equal, one who undertakes the treatment of a case of acute osteomyelitis may be forgiven if his treatment is a little too radical, but may not be forgiven if his treatment is insufficient. Among his conclusions, Cutting states "If, in a given case, there is doubt as to whether operation should be performed or not, a safe rule to follow is to paraphrase an aphorism coined with respect to drainage in abdominal surgery—when in doubt, operate."

Pyrah and Pain also advocate early radical surgery, reporting a 29 per cent mortality in 176 cases, and a 27 per cent mortality in 262 cases.

Buzellow, in 1928, advocated chiseling open the marrow cavity as soon as possible, and believes that blood stream infection or general sepsis can be avoided only by the early evacuation of pus. He states that the results in his clinic compare favorably with those in which the marrow cavity was not opened. Other authors, advocating early drainage of the bone, regardless of the patient's condition, express essentially the same views as those quoted.

Among those favoring conservative measures may be mentioned Philipowicz, who believes that the treatment depends upon whether the course of the disease from the beginning has the distinct character of an acute, severe infectious disease, or is that of a localized and more or less circumscribed bone disease, and that treatment should be basically conservative without opening the bone, abscesses to be merely incised. He is of the opinion that

the problem in the acute stage cannot be solved by operation alone, and advocates the use of serum and vaccine from the onset

Miller and Smith-Petersen, reporting a series of 90 cases, state that they are becoming more conservative in their treatment of the acute cases, and attack the local lesion only after the patient's condition has been rendered as favorable as possible. Should an abscess be present, it is merely incised, and where pus in the bone is suspected, they only drill a few holes.

Wilson and McKeever, reporting 90 cases, with 12.2 per cent mortality, are of the opinion that operation may be performed too early rather than too late. Of 24 patients having early adequate drainage within seven days of the onset of the illness, 25 per cent died. These showed no microscopic evidence of osteomyelitis. When operation was delayed until between the seventh and twenty-eighth day, the mortality was 9.7 per cent. In 23 cases of spontaneous drainage, there was only one death. Of the 24 cases operated upon in the early stages of the disease, 37.5 per cent developed metastatic lesions. In their summary, they state that operation should be delayed until the child is in the best condition (one, two or three days), and that, in a blood borne infection, the lesion should be allowed to localize. If operated upon too early, a fatality may result, as in incision in cases with brawny cellulitis.

Leveuf states that, in his experience, late intervention as a rule gave better results than early operation, and believes that the criterion of progress is the temperature and blood culture. He found that a septicemic state was of no grave prognostic significance, for in all of his cases in which operation was not performed, early spontaneous recovery ensued and no foci developed. He found that a subperiosteal abscess usually forms as the temperature falls and is related to a central focus in the diaphysis and that early surgery establishes a communication between the focus in the bone containing virulent organisms and toxins, and parts of the body in which the defense mechanism is not yet established. He found that late intervention does not aggravate the osseous lesions or process of sequestration. He further states that the advantage of conservative treatment cannot be over emphasized, and that vaccine therapy should be administered.

Crossan presented the results of early and late intervention in a series of cases, in which the lower mortality was decidedly in favor of conservative treatment.

As a working method in deciding upon the form of treatment indicated in specific cases, the classification of Wilensky forms a satisfactory guide. Group I. Cases in which operation of any kind can be avoided. These, with their subgroups, consist essentially of the milder forms of the disease. Group II. Includes those cases in which the general infection is the paramount factor and determines the fatal end-result. This is the most virulent group, and operation can be of little avail. Group III. Those cases in which the general infection becomes controlled and the end-result depends entirely on the local lesion or any intercurrent complication or associated lesion. Group

IV That in which the general infection becomes controlled and the end-result depends entirely on the local lesion in the bone

Unfortunately, the data as presented in the histories of the present series are not sufficient to enable us to classify our cases in accord with the above suggestion, and in a series such as this, collected from various hospitals, it has been necessary to arbitrarily establish certain criteria, especially as this communication deals chiefly with the clinical aspects of the condition

With this in mind, and appreciating its limitations, we wish to present the results of our studies from the following aspects

I The outcome (survived or died) in relation to (1) The age of the patient, (2) the degree of toxicity of the patient at the time of operation, described as very toxic, or slightly so, (3) the operative procedure employed, whether (a) mere incision or aspiration, (b) drill, or (c) gouge or guttering of bone, and (d) time of operation. A patient was arbitrarily regarded as being toxic when the temperature was over  $102^{\circ}$  F, with corresponding increase of pulse rate and leukocytosis, and presented the general appearance of toxemia. Operation was classed as immediate, when performed within 48 hours of making the diagnosis, and delayed, when performed at any time after the second day

II The results in relation to (1) Type of organism, (2) with reference to the time of operation, (a) early, (b) delayed, (3) the operative procedure, whether the bone was opened by drill or gouge, or merely aspiration, incision, or no surgical procedure, (4) the site of the infection, whether (a) only in the original site, (b) in the blood stream alone, (c) primarily in the original site and blood stream, or (d) primarily in the wound and secondarily in the blood stream after operation

III The formation of secondary foci and the outcome in reference to (1) The type of organism, (2) the time of operation

IV The outcome in reference to (1) The age of the patient, (2) the bone involved, and (3) the time of operation

V The formation of sequestra as related to (1) The time of operation, and (2) the type of infecting organism

Table I shows, that of 17 cases under three years of age, six were very toxic when operated upon. Of these, immediate drilling was performed in one case, with recovery, the bone was opened twice with a gouge, with recovery, delayed drilling was performed in three instances, with recovery, and one child who died was so ill that no operative procedure was attempted. Of the children under the age of three, who were only slightly toxic when seen, drilling was performed immediately in one and gouging in two, all of whom lived. In the delayed group, drilling was performed in two, and the gouge used in five, all of whom survived

Between the ages of three and nine, the statistics for the very toxic group, with immediate operation, were 11 drilled and 14 gouged, of whom one drilled and six gouged died. Four, who were not operated upon or incised, lived and two died. In this age group (three to nine), when the patient was only slightly



TABLE I

RESULTS OF IMMEDIATE AND DELAYED OPERATIONS IN REFERENCE TO AGE, DEGREE OF TOXICITY, AND OPERATIVE PROCEDURE

Age	Toxicity	Operative Proce- dure	Immediate Operation		Delayed Operation		Not Operated, Incised, <i>etc</i>	
			Lived	Died	Lived	Died	Lived	Died
Under 3 yrs	Very	{ Drill	1		3			1
		{ Gouge	2					
	Slight	{ Drill	1		2			
		{ Gouge	2		5			
3-9	Very	{ Drill	10	1	2		4	2
		{ Gouge	8	6	3	1		
	Slight	{ Drill	5		2		6	
		{ Gouge	6	1	10			
10-14	Very	{ Drill	2	10	2		1	
		{ Gouge	13	2	1	2		
	Slight	{ Drill	3		1		4	
		{ Gouge	4		7			
15-19	Very	{ Drill			1			
		{ Gouge	1	3	1			
	Slight	{ Drill			1			
		{ Gouge	2		6			
Over 20	Very	{ Drill				2		
		{ Gouge						
	Slight	{ Drill						
		{ Gouge	1		5	1		
Totals			61	23	52	6	15	3

	Number of Cases	Deaths	Percentage Mortality
Very toxic, immediate operation—drill	24	11	45 8
Very toxic, immediate operation—gouge	35	11	31 4
Slightly toxic, immediate operation—drill	9	0	0
Slightly toxic, immediate operation—gouge	16	1	6 2
Very toxic, delayed operation—drill	10	2	20 2
Very toxic, delayed operation—gouge	8	3	37 5
Slightly toxic, delayed operation—drill	6	0	0
Slightly toxic, delayed operation—gouge	34	1	2 9
No operation, toxic	18	3	16 6
Totals	160	32	

toxic, and was immediately operated upon, of those who survived, five were drilled, with no mortality, and of the seven in whom the gouge was employed, one died. When operation was delayed in the slightly toxic, of those who

lived, six were aspirated or incised, two drilled and ten gouged, with no mortality

Between ages 10 and 14 Very toxic, immediate operation—two drilled and 13 gouged, survived, while 10 drilled and two gouged, succumbed Very toxic, delayed operation—two drilled and one gouged, survived, while two gouged, died Slightly toxic, immediate operation—the three drilled and four gouged, all survived Slightly toxic, delayed operation—one drilled, seven gouged and four incised or aspirated, all survived

Between ages 15 and 19 Very toxic, immediate operation—of the four upon whom the gouge was used, one lived and three died Delayed operation in this group showed one gouged and one drilled, with no mortality Slightly toxic, immediate operation—two gouged, lived, no mortality Delayed operation—one drilled and six gouged, lived, no mortality

Over 20 years of age The only two very toxic cases, who were drilled late died, and of those only slightly toxic, one immediate operation, gouge, lived and of the delayed operations, gouge, five lived and one died

TABLE II

MORTALITY PERCENTAGE OF ENTIRE GROUP IN REFERENCE TO CONDITION OF PATIENT, AND TIME OF OPERATION

		Deaths*	Lived	Percentage Mortality
Toxic	Immediate operation	22	37	37.3
	Delayed operation	5	13	27.7
Nontoxic	Immediate operation	1	24	4.0
	Delayed operation	1	39	2.5

\* Not included in above summary

Two moribund on admission—not operated upon

One death from hemorrhage upon removal of sequestrum, 3 yrs later

One death from hemorrhage upon removal of sequestrum, 3½ mos later

Deaths from hemorrhage (several) on thirty-ninth day

Table II gives the summary of the fatalities in this series, and contrasts immediate versus delayed operation (disregarding the operative procedure), in the toxic and nontoxic patient, regardless of age, type of organism or operative proceeding and shows that in 59 toxic patients, upon whom immediate operation was performed, 37 lived and 22 died, a mortality of 37.3 per cent, while of the 18 toxic cases, in whom operation was delayed, 13 lived and 5 died, a mortality of 27.7 per cent. In the nontoxic patients, of the 25, upon whom immediate operation was performed, 24 lived and one died, the figures for the delayed, nontoxic, total 40, of whom 39 lived and one died, a mortality of 2.5 per cent. Not included in the above figures are two patients who were moribund on admission and upon whom no operative procedure was performed, two who died from hemorrhage upon removal of a sequestrum, one, three years, and one, three and one-half months after the original operation, and one patient, who died on the thirty-ninth postoperative day as a result of uncontrolled hemorrhage. A consideration of the above statistics

does not leave much room for doubt that, at least in this series, immediate operation in the very toxic patient showed a higher mortality, in contrast to those instances in which operation was delayed

In only two instances did the records show that upon admission the patients were moribund and any operative procedure considered inadvisable, while upon several occasions the notes stated "patient moribund—operation—death within a few hours"

TABLE III

OUTCOME IN REFERENCE TO DEVELOPMENT OF SECONDARY FOCI, THE TYPE OF ORGANISM, AND TIME OF OPERATION

	DEVELOPED FOCI						DID NOT DEVELOP FOCI					
	Early Operation		Delayed Operation		Not Operated Upon Aspirated or Incised		Early Operation		Delayed Operation		Not Operated Upon Aspirated or Incised	
	Lived	Died	Lived	Died	Lived	Died	Lived	Died	Lived	Died	Lived	Died
Staphylococcus	19	7	7	1		1	42	11	13	3		3
Streptococcus	5	1					5		2			
Others or mixed							2					
Not recorded or no growths	2	2	1				9	1	13	1		1
Totals	26	10	8	1		1	58	12	28	4		4
Totals	36		9			1	70		32			4
Died	10		1			1	12		4			4
Mortality percentage	27.7		11.1			100	17.1		12.5			100

## SECONDARY FOCI

Developed	Early Operation	Delayed Operation
Yes	36 (33.9%)	9 (21.9%)
No	70 (66.1%)	32 (78.1%)

Among the reasons advanced for the early surgical interference is that by so doing, there is a decrease in the number of secondary foci which may develop. Table III shows that of the cases in which, regardless of the degree of toxicity, it could be ascertained from the notes as to whether or not such foci developed, these occurred in 33.9 per cent of the cases in which operation was performed early, and in 21.9 per cent of the cases in which it was delayed. Of the 36 cases developing secondary foci, who were operated upon early, 10 died, a mortality of 27.7 per cent, while of the nine who were operated upon later, only one died, a mortality of 11.1 per cent. Of the 70 cases who were operated upon early, and who did not develop secondary foci, 12 died, a mortality of 17.1 per cent, and of the 32 who did not develop secondary foci and were operated upon later, four died, a mortality of 12.5 per cent. From the above it will be seen that early operation does not tend to prevent the development of secondary foci, and when such foci appear, the mortality is 27.7 per cent in contrast to 11.1 per cent when such foci appear following the delayed operation. When there were no secondary foci, the

TABLE IV  
MORTALITY IN REFERENCE TO PRIMARY BONE INVOLVEMENT, AGE OF PATIENT, AND TIME OF OPERATION

	HUMERUS				RADIUS OR ULNA				FEMUR				TIBIA				TIBULA			
	Not Op, or Asp, Inc		Early Op		Not Op, or Asp, Inc		Early Op		Not Op, or Asp, Inc		Early Op		Not Op, or Asp, Inc		Early Op		Not Op, or Asp, Inc		Early Op	
Age	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D	L	D
Under 3 yrs	1		2				1		1	5			1	2			1	1		
3-9	2				2	1	3		11	2	6	1	2	1	14	6	7	2	4	
10-14	1	1					1		5	3	6	1	2		15	7	3	1	3	
15-19		1	1				1	2	1	2	4				1		3		2	
Over 20			2	1					1	1	3				3					
Totals	4	2	5	1	2	1	4	0	2	0	0	0	19	7	22	5	4	1	31	13
Died																				
Mortality percentage																				

Totals	15																			
Died	4																			
Mortality percentage	26.6																			

FEMUR—Early operation,	26 total,	7 deaths,	26.9% mortality
Delayed operation,	27 total,	5 deaths,	18.5% mortality
Aspirated or incised,	5 total,	1 death,	20% mortality

TIBIA —Early operation,	44 total,	13 deaths,	29.3% mortality
Delayed operation,	18 total,	0 deaths,	0% mortality
Aspirated or incised,	4 total,	1 death,	25% mortality

mortality of early interference was 17.1 per cent in contrast to 12.5 per cent when delayed.

Table IV shows the age of the patient, the primary bone involved, the time of operation, and the end-result. It will be seen that the femur and tibia were the bones most frequently involved, and in the 26 instances in which early operation was performed upon the femur, there were seven deaths, a mortality of 26.9 per cent, while of the 27 delayed instances, there were five deaths, 18.5 per cent mortality. The statistics for the tibia are even more striking, for in the 44 cases with early operation there were 13 deaths, a mortality of 29.3 per cent, while in 18 in which operation was delayed, there were no deaths.

TABLE V

FORMATION OF SEQUESTRA IN REFERENCE TO TYPE OF ORGANISMS AND TIME OF OPERATION

Time of Operation	Organism	Sequestra Re- moved		Percentage Developing Sequestra
		Yes	No	
Early	Staphylococcus	17	53	24.2
	Streptococcus		5	0
	No growth or not stated	3	8	27.2
	Other or mixed		3	0
Delayed	Staphylococcus	16	30	34.7
	Streptococcus		4	0
	No growth or not stated	1	8	11.1
	Other or mixed		1	0
No operation, aspirated or incised	Staphylococcus	1	5	16.6
	Streptococcus		1	0
	No growth or not stated		4	0
	Other or mixed			

## SEQUESTRA

Operation	Developed	
	Yes	No
Early	20	69
	22.4%	77.5%
Later	17	43
	28.3%	71.5%
Not operated upon	1	10
	9.1%	90.9%

The statistics were studied with regard to the formation of sequestra, in conjunction with the time of operation and the invading organism, and Table V shows that the time of operation had but little effect on the formation of sequestra—22.4 per cent in the early cases and 28.3 per cent in the late. As was to be expected, the Staphylococcus was the most frequently encountered organism. The outcome was studied from the viewpoint of the operative procedure, whether the bone was opened by drill or gouge, as related to the time of operation and the condition of the patient. Table VI

# HEMATOGENOUS OSTEOMYELITIS

TABLE VI

	Number of Cases	Deaths	Percentage Mortality
Very toxic, immediate operation—drill	24	11	45.8
Very toxic, immediate operation—gouge	35	11	31.4
Slightly toxic, immediate operation—drill	9	0	0
Slightly toxic, immediate operation—gouge	16	1	6.2
Very toxic, delayed operation—drill	10	2	20.0
Very toxic, delayed operation—gouge	8	3	37.5
Slightly toxic, delayed operation—drill	6	0	0
Slightly toxic, delayed operation—gouge	34	1	2.9
No operation	18	3	16.6
Totals	160	32	

shows that in the very toxic, a higher mortality accompanied immediate drilling of the bone, 45.8 per cent, than when the gouge was used, 31.4 per cent, the difference probably being due to the more toxic state of the patient when the drill was employed. When the operation was delayed in the very toxic, the mortality percentages were reversed, the drill being 20 per cent and the gouge 37.5 per cent. When the patient was only slightly toxic, immediate drilling was resorted to nine times, without a fatality, and the gouge employed 16 times with one fatality, 6.2 per cent, while when the patient was only slightly toxic and operation delayed, in six instances the bone was drilled without fatality, and opened by gouge 34 times with one fatality, 2.9 per cent. When the operative procedure was incision, aspiration or no surgical interference, three of 18 cases died, a mortality of 16.6 per cent. In this latter group are included the two who were moribund when first seen and who died within a few hours of admission to the hospital. From an analysis of the above table, it is again evident that surgical interference in the very toxic patient, whether immediate or delayed, and regardless of the procedure adopted, is accompanied by a much greater mortality than when surgery is postponed until the patient is no longer in a toxic condition—33.6 per cent contrast to 2.2 per cent, it being fully realized, however, that some patients are so overwhelmed by their toxemia that they will succumb in spite of any form of treatment.

Table VII shows the elapsed time, in the fatal cases, between operation and death, in reference to the age of the patient, the degree of toxicity when operated upon and the time of operation. The two cases, which were moribund on admission and which were not operated upon, are not included. It will be seen that the greatest number of fatalities occurred within the first four days, all but one of which were in the toxic group who were immediately operated upon. In the three cases dying from hemorrhage, one month or longer after operation, the condition of the patient and time of operation probably had but little bearing on the outcome, but they are nevertheless included. The conclusion to be drawn from the statistics in this table is that the toxic patient immediately operated upon was not afforded sufficient opportunity to combat the infection. The only two fatalities in the nontoxic, de-

TABLE VII

ELAPSED TIME BETWEEN OPERATION AND DEATH IN REFERENCE TO AGE, CONDITION OF PATIENT, AND TIME OF OPERATION

Age	Condition	Time of Operation	Interval Between Operation and Death									
			Days							2nd Week	3rd Week	Over 3 Weeks
			1	2	3	4	5	6	7			
Under 3 yrs	Toxic	Immediate	1									
		Delayed										
	Nontoxic	Immediate										
		Delayed										
3-9	Toxic	Immediate		2	2	1					1	2
		Delayed								1		
	Nontoxic	Immediate					1					
		Delayed									1	
10-14	Toxic	Immediate	4		3	1		1		2		1
		Delayed										
	Nontoxic	Immediate										
		Delayed										
15-19	Toxic	Immediate	1	1								
		Delayed										1
	Nontoxic	Immediate										
		Delayed										
Over 20 yrs	Toxic	Immediate										
		Delayed			1							1
	Nontoxic	Immediate										
		Delayed										1
Totals			6	3	6	2	1	1	0	3	2	6

Two cases moribund on admission—not operated upon—not included

One died from hemorrhage upon removal of sequestrum, 3 yrs later

One died from hemorrhage upon removal of sequestrum, 3 mos later

One died from multiple hemorrhages, upon removal of sequestrum, 39 days later

	Days							Weeks		Over 3 Weeks	
	1	2	3	4	5	6	7	2	3		
Toxic, immediate	6	3	5	2	1	1	0	2	1	3	} 28 Total
Toxic, delayed	0	0	1	0	0	0	0	1	0	2	
Nontoxic, immediate											} 2 Total
Nontoxic, delayed								1		1	
Totals	6	3	6	2	1	1	0	3	2	6	

laid operation group, occurred as a result of secondary hemorrhage in the third week or later

# HEMATOGENOUS OSTEOMYELITIS

An attempt was made to evaluate the hospital morbidity in the series, but in view of the fact that there was no basis of estimating how long the patients should be hospitalized, this attempt was abandoned. The records showed that in many instances a patient was readmitted one or more times for involvement of the original or other sites, but in the series being reported, only the first admission was considered.

TABLE VIII

OUTCOME IN REFERENCE TO LOCATION OF INFECTION, ORGANISM, AND TIME OF OPERATION

Organism	Time of Operation	Wound Only		Blood Only		Both Primary		Primary Wound Secondary Blood	
		Lived	Died	Lived	Died	Lived	Died	Lived	Died
Staphylococcus	Early	34	6			7	6	8	9
	Delayed	39	1			2	4		1
	Not operated upon or incised	5		1			1		
Streptococcus	Early	3						1	
	Delayed	2				1		1	
	Not operated upon or incised								1
Other or mixed	Early	3							1
	Delayed								
	Not operated upon or incised								
Totals		86	7	1	0	10	11	11	11
No organism, or not recorded	Early	7	1						
	Delayed	8	1						
	Not operated upon or incised	1	1						
Totals		16	3						

Wound only Incised, 5 cases—all lived

Wound only Early operation, 46 cases—6 died—13 % mortality

Wound only Delayed operation, 42 cases—1 died—2 3 % mortality

Both primary Early operation, 13 cases—6 died—46 1 % mortality

Both primary Delayed operation, 7 cases—4 died—57 1 % mortality

Primary Wound—Secondary Blood Early operation, 19 cases—10 died—52 6 % mortality

Primary Wound—Secondary Blood Delayed operation, 2 cases—1 died—50 % mortality

Table VIII shows the results in reference to the site of the primary infection, in relation to the type of organism, and to the time of operation. It will be seen that in the majority of cases in which the organism was identified, when the infection was confined to the original focus (93 cases), there were seven deaths, a 7 5 per cent mortality, regardless of the time of operation. In this group of the 46 cases subjected to early operation, six died, a mortality of 13 per cent, while of the 42 with delayed operation, one died, a mortality



of 23 per cent. Of the five in this group, in which the operative procedure was limited to incision, there were no deaths. When the infection was primary in both blood stream and bone, of the 13 operated upon early, six died, a mortality of 46.1 per cent, and of the seven who were operated upon later, four died, a mortality of 57.1 per cent. When the infection was primarily in the wound and the blood stream showed involvement after early operation, 10 of the 19 cases operated upon died, a mortality of 52.6 per cent. In the two cases of primary wound and secondary blood stream infection following delayed operation, the mortality was 50 per cent.

The above statistics would tend to show that when the infectious process was confined to the primary site the mortality was considerably less when operation was delayed than when performed early, 23 per cent as compared to 13.9 per cent. When the blood stream was involved together with the bone at the time of operation, the mortality was exceptionally high, regardless of the time of operation—46.1 per cent for early and 57.1 per cent for late.

While it is generally agreed that the Orr method of treatment, or some modification of it, affords the best results after the bone has been drained, a careful follow-up record in this respect was not obtained in the present series in a sufficient number of cases to warrant an opinion based on statistics. No attempt was made, therefore, to estimate the morbidity as related to the various methods of treatment adopted, but in our own experience the method advocated by Orr has given greater satisfaction than any other.

In a small proportion of cases, too few to warrant classification, various types of vaccine and bacteriophage were administered, but an estimation of their efficacy would be of doubtful value from the data supplied. Likewise, even though blood transfusions, both single and multiple, large and small, were given in many cases, one would not be justified in evaluating their effect in view of the many other factors encountered in each case. As a general impression, not verified by statistical evidence, we feel that repeated, small blood transfusions are well worth while, as if properly given, apparently they can do no harm and might be of considerable assistance in rendering the patient better able to overcome his infection.

In view of the fact that the old saying still holds that experience is a hard task master, and also that we learn most from our mistakes, a very brief comment on some of the fatalities which occurred might be of interest. A female, age 13, treated for rheumatism for five weeks before the osteomyelitis was suspected, died of shock when a sequestrum was removed from her femur, three and one-half months after the original operation. The notes state that her hemoglobin was never above 52 per cent until just after a transfusion which preceded the sequestrectomy, and "at this date it looks as though earlier and frequent transfusions might have saved her."

A boy, age 12, moribund on admission, three days after onset, was immediately operated upon. The notes state "Operation (drill) very short, only 15 minutes. Death next day." This was obviously a case in which no improvement could be hoped for from surgery.

A boy, age 14, moribund on admission, had his femur opened by gouge when he did not show signs of improvement two days after admission, and postmortem, four days later, showed metastatic abscesses of all organs. The blood culture showed *Staphylococcus aureus*.

A girl, age 11, very toxic on admission, had her tibia immediately opened by drill, and postmortem, three days later, showed purulent pericarditis, peritonitis, and multiple abscesses of the cortex of her kidneys.

A very toxic boy, age 11, with involvement of the tibia, was operated upon as an emergency (drill) and the notes state "Postoperative temperature went up to 106° F and did not fall after operation but went to 107° F. Delirious all during first postoperative day and unconscious the next, up to time of death."

An interesting observation regarding the temperature in the toxic patients upon whom early operation was performed, was the fact that the supposed relief of tension in the bone was but rarely followed by a drop in temperature, in many instances the tendency being rather to either show no effect, or an elevation. We regret that our statistics do not include a sufficient number of temperature recordings to warrant including them, but our observations in this respect are in accord with those of Wilensky.

A man, age 22, very toxic on admission, who had injured his femur three days previously before operation showed a *Staphylococcus* blood stream infection of 15 colonies per plate. He was operated upon two days after admission and a postmortem blood culture taken 14 hours after operation showed "innumerable *Staphylococci*." Incidentally, his temperature before operation was 103° F and after operation it went to 108° F, the pulse being 100 and 150, respectively. It is believed that this case exemplifies those instances in which the toxic patient's resistance is overwhelmed by increasing the blood stream infection.

A boy, age six, very toxic, was treated expectantly for nine days before a diagnosis of involvement of his femur was made. As soon as the condition was recognized, in spite of being acutely ill, he was operated upon and the operation notes are rather significant. "At operation, the whole thigh contained pus, coming from beneath the periosteum. The roof of the femur was removed and the patient promptly died of shock, as might have been anticipated." It is indeed unfortunate that the diagnosis of osteomyelitis was made in this instance, as otherwise he might have had an opportunity to handle his infection, as he was apparently doing.

In acute hematogenous osteomyelitis, the primary consideration is naturally to save the life of the patient and secondarily to effect a recovery as soon as possible, with a minimum of deformity, residual infection or damage to other parts of the body. It is with this thought in mind that, in the present series, we have, therefore, stressed rather those factors influencing the mortality rather than the morbidity of the condition, and from a résumé, one gathers the following impressions:

## CONCLUSIONS

(1) Immediate operation with opening of the bone, whether by gouge or drill, upon diagnosis of acute osteomyelitis in an acutely toxic patient, is accompanied by an unjustified mortality, and should the patient survive it is probably in spite of, rather than because of surgery

(2) During the acute stage rest and supportive measures alone should be adopted till the defense mechanism of the body has had time to develop

(3) When surgery is indicated, it should be performed with as little disturbance to the part involved as is consistent with attaining its objectives

(4) The development of secondary foci increases the mortality appreciably, when they do appear, they are more apt to do so in cases that were operated upon early rather than late

(5) A demonstrable blood stream infection greatly increases the mortality

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## CYSTIC DISEASE OF THE SPLEEN

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IN THE American literature, reported cases of cystic disease of the spleen are quite rare. In a comprehensive article, Fowler<sup>1</sup> collected 86 cases of nonparasitic cystic disease, reported up to 1912. In 11 the diagnosis was made by trocar. Twenty-eight were found at postmortem. Other articles,<sup>2-3</sup> in 1913 and 1924, brought the record cases up to 90. Our interest in this subject was aroused by the surgical removal by one of us of an enormous spleen containing multiple cysts, the etiology of which is somewhat obscure. Cysts of the spleen may be classified as dermoid, parasitic and nonparasitic. The spleen may contain one or two solitary large cysts or a great number of small cysts. The latter is quite rare, there being only 10 cases of this type recorded with adequate microscopic reports.

Exclusive of dermoid and parasitic types, splenic cysts are classified by Fowler<sup>1</sup> on an etiologic basis as follows:

### I True Cysts

- (1) Infestation cysts (inclusion of peritoneum, inflammatory or traumatic, small and multiple, superficial or deep [malaria and leishmaniasis])
- (2) Dilatation cysts. Polycystic disease of the spleen. The entire parenchyma studded. Rare. Ectasia of the splenic sinuses.
- (3) Neoplastic cysts. Lymphangioma, hemangioma. Differentiation from inflammatory types may be difficult. Sarcomatous metastases.

### II Pseudocysts—Secondary

- (1) Traumatic. Origin usually from a hematoma. Usually large and unilocular. Contents serous or hemorrhagic.
- (2) Degeneration cysts. Arising from secondary changes in infarcted areas from arterial degeneration or occlusion of blood vessels by emboli with subsequent necrosis of splenic pulp. Usually solitary and large.

Cystic disease in the spleen may present four morphologic types:

- (1) A large solitary cyst. Contents usually hemorrhagic.
- (2) Numerous very small cystic cavities, usually subcapsular or projecting from the capsule. This is the most usual type.
- (3) The so-called multiple or polycystic spleen in which the entire parenchyma is studded. Seven cases of this type are recorded. Fowler,<sup>1</sup> Leudet,<sup>4</sup> Coenen,<sup>5</sup> Suchanek,<sup>6</sup> Lubarsch,<sup>7</sup> Le Fort Le-

gen,<sup>8</sup> Dobrzaniecki<sup>10</sup> The present case makes the eighth reported

- (4) One large cystic cavity involving only part of the parenchyma, which is well preserved, with numerous small cystic satellites (Howald,<sup>11</sup> Mondre,<sup>12</sup> Brandberg<sup>9</sup>)

Many published cases give no histologic details and the exact nature of the cystic disease remains obscure The following is a selected list of reported cases of cystic disease of the spleen of the above types probably not of neoplastic, dermoid, or parasitic nature

Leudet,<sup>4</sup> 1853 One cavity divided into four to five partitions by fibrous membranes lined by pavement epithelium

Boettcher,<sup>13</sup> 1870 Multiple "pea-sized" serous cysts which are lined by endothelium

Matter,<sup>13</sup> 1885, male, age 68 An enlarged spleen weighing 370 Gm Four-fifths of the splenic parenchyma was filled by a large cyst covered in part by a thin rim of splenic parenchyma Walls were hard, cartilaginous and calcified Surrounding this were 17 satellites varying from the size of a "hemp seed" to a "large nut"

Fink, quoted by Coenen,<sup>5</sup> 1890, male, age 48 Spleen enlarged and filled with numerous cystic cavities, endothelium lined

Coenen,<sup>5</sup> 1910 A multilocular cyst and other numerous cysts of varied size, from "millet seed" upwards, weight 2,565 Gm Size 33x20x10x10 cm The spleen was removed during pregnancy The surface was knobbed The walls of the cyst were thin, transection revealed a honeycomb appearance, the parenchyma being riddled with numerous smooth-walled cysts of various sizes, contents clear or bloody, thin fluid Very little normal parenchyma remained Microscopy revealed blood and lymph sinuses of various sizes Smaller ones unlined, the larger lined by endothelium Coenen believed this to be a case of multiple lymphangiectasia of the spleen

Fowler,<sup>1</sup> 1912, female, age 22 Abdominal trauma one year prior to the delivery of twins Splenectomy performed following delivery because of large abdominal mass Spleen weighed 385 Gm Size 20x11x6 cm A fibrous band divided the spleen into two complete parts Entire organ was cystic, containing large and small cavities filled with jelly-like substance Microscopy suggested dilatation of numerous lymph sinuses Some were lined by endothelium

Suchanek,<sup>6</sup> 1912 A large cystic spleen with one cyst, size of a child's head, and other smaller ones, contents clear, serous, bloody or purely hemorrhagic Contents of varied reaction and specific gravity No residual splenic tissue Case described as cystic lymphangiectasia

Bacigalupo and Giosso,<sup>13</sup> 1919 Multiple serous cysts in an infant found at postmortem

Adrian Lambert<sup>14</sup> 1919, female, age 34 Spleen removed at operation measuring 9x8x6 cm Two cystic cavities communicating Contents clear

amber fluid "Lining smooth, shining," old thrombosed blood vessels found Lambert believed the amyloid degeneration of blood vessels to be the etiologic agent

Alfejew,<sup>15</sup> 1923 Reported cases of multiple small cysts of the spleen said to be due to dilatation of lymphatic channels Two types were encountered

- (1) Lymphangiectasias These appear deep in normal splenic tissues and consist solely of an alteration of the splenic tissues
- (2) Lymphangiomata Usually dilatations distinct from normal splenic parenchyma

Howald,<sup>11</sup> 1926 Collected a series of 73 cases of cystic spleens from the literature In only 18 cases could relations with blood vessels or lymph vessels of the spleen be traced In many cysts a distinct endothelial lining was described In the remaining 56 these relations were absent and the cysts were unlined In the large cysts lining cells were flat and high, in the small cysts a close formation of blood vessels was described Howald emphasized that the delicate endothelial lining of cystic spaces might be frequently lost during manipulation, and that the lining of lymph vessels may be transformed to cuboidal epithelium He states that adhesive cysts arise frequently from hematomata on the basis of histogenetic defects

Mondre,<sup>12</sup> 1926, female, age 43 Large cystic spleen, weight 3.15 kilos There was one large cystic cavity and numerous others "peanut to "walnut" in size The larger cysts were lined by endothelium In the smaller cysts epithelium was flattened to cuboidal Splenic tissue showed pressure atrophy between the cysts

Lubarsch,<sup>7</sup> 1927, female, age 41 Spleen weighed 1,320 Gm Size 21x14x12 cm The capsule was thick, dense and fluctuant in some areas Section revealed about one dozen cavities, mostly rounded, size of a "walnut," and many smaller cavities, with smooth walls Contents fluid or semisolid Between the cavities was more solid, nodular material, dark red or grayish-yellow in color Residual splenic tissue present only in outer layer, varying from 0.5 to 2.5 cm in width *Microscopic Examination* The large cavities contained partly homogeneous and apparently filamentous network with occasional red blood cells, and fat-filled phagocytes The walls of larger cavities consisted chiefly of hyaline delicate connective tissue, without definite lining cell layers The smaller, more spherical cavities had a definite cell lining and homogeneous contents containing red blood cells There were solid nodules of various sizes, gray to dark red in color These represented cavities filled by extravasated blood and lymph material which had become organized by numerous fibroblasts and angioblasts At the upper pole, there was splenic tissue showing similar pictures, except that in some areas the follicles were completely absent and the pulp capillaries and arteries were hyalinized and showed amyloid degeneration In the large splenic rests were abundant and large lymph follicles with arteries partially hyalinized with amyloid *Pathologic*

*Diagnosis* "These are cystic lymphangiomata and hemangiomata, or mixtures, with organization of solid nodules by numerous blood vessels Amyloid deposition is atypical, as is associated with a diffuse deposit of hyalin in the spleen material Relation between hyalin and amyloid material and cyst formation is indefinite"

The case of Le Fort Legen<sup>8</sup> was probably of sarcomatous nature Sections showed dense connective tissue There were many cysts, most of which showed no epithelial lining

Brandberg,<sup>9</sup> 1928 Case 1 No history Spleen with one cyst, size of a "hazel nut," surrounded by multiple conglomerate satellites Rest of splenic tissue normal All cavities lined by endothelium and filled with gelatinous substance Believed to be a case of congenital multiple lymphangiectasia, the result of ectopic lymph vessels

Dobrzaniecki,<sup>10</sup> 1930, female, age 38, who suffered an acute abdominal episode, characterized by tenderness in the right upper quadrant and high temperature, following a severe trauma One month later a large spleen was removed, measuring 25x13x14 cm The lower portion was made up of multiple noncommunicating, large smooth-walled cysts, containing 140 cc of yellow fluid and blood clots Microscopically the tissue between the cysts was a homogeneous and necrotic mass containing fibrin Blood vessels showed endothelial thickening and narrowing of the lumen Some small vessels were obliterated No hemosiderin was present The author attributes the cavitation to trauma and ischemic necrosis caused by obliterative endarteritis

Females are predisposed to the development of cystic disease of the spleen Of 68 cases in which the sex was stated, 40 were females (Fowler<sup>1</sup>) This is most likely because of the periodic variations in size occurring in the spleen during the menstruation and pregnancy<sup>13a</sup> During these periods the spleen may become enlarged and congested and when subjected to trauma or vascular insults, hematoma and cystic disease follow Bircher<sup>16</sup> studied 54 cases of cystic spleen and attributed 17 to traumatic causes One case was discovered during pregnancy Subsequent operation disclosed a large cystic spleen due probably to a twisted pedicle, the result of trauma The cystic tumor may increase in size following delivery, and necrosis frequently occurs (Routier-Wells<sup>13</sup>) Coenen<sup>5</sup> removed a polycystic spleen during pregnancy Dowd<sup>17</sup> incised a large cystic spleen postpartum There was a history of trauma The walls were necrotic "almost the entire spleen came away in sloughs" Trauma is a very important factor In many cases, cystic spleens have apparently resulted from abdominal blows delivered as long as ten years prior to the operation Eventually, infarction, hemorrhage and cyst formation, usually of the solitary type, occurs Case 2 of Hamilton and Boyer<sup>18</sup> apparently resulted from an abdominal blow delivered four years prior to removal of a spleen measuring 15x15x8 cm containing a large solitary hemorrhagic cyst Traumatic hemorrhagic cysts may contain as much as ten liters of fluid<sup>1</sup> On the other hand, enormous cysts of the spleen may develop without a history of trauma, as in our case and that of Gosselin<sup>19</sup> In the

latter, a spleen containing a collapsed cyst the size of a "football," and containing three liters of fluid, was removed from a middle-aged female. There was a partial obliteration of the splenic artery.

Nineteen of Fowler's<sup>1</sup> series of 44 cases probably were of traumatic origin—five from disintegration (infection and arterial degeneration), eight were cysts into which secondary hemorrhage had occurred, two were neoplastic. Usually the single, large, unilocular cyst originates secondary to intraparenchymal or subcapsular hemorrhages. Later the cellular contents are deposited upon the lining wall and the fluid eventually becomes serous and clear. Possibly many unilocular solitary cysts originate from fusion of smaller cavities. Often trabeculated projections into cyst cavities are suggestive of multiple, broken-down septa. Even many small cysts are multilocular at onset, although they appear single. The cyst wall is usually thin and often formed by only a very thin capsule.

The huge spleens of malarial and syphilitic patients are likely to be injured by hematoma and cyst formation. Perisplenic adhesions are prone to occur in hyperplastic spleens. Perisplenitis and cyst formation are apparently related. Hemorrhagic cysts occur in Arabs, due to ruptures restricted by adhesions.<sup>1</sup> In typhoid fever, rupture of a distended capsule might possibly result in cyst formation. Numerous small multiple surface cysts in malarial splenomegaly are described (Subbotic<sup>13</sup>). This author attributes the surface cysts to rupture of the splenic capsule over the distended pulp. Cystic spleens occur in pemphigus (Bednor<sup>13</sup>) and mumps (Feral<sup>13</sup>) and in syphilis (Harnett<sup>13</sup>). The latter is due to endarteritis with rupture of intrasplenic blood vessels.

Boettcher<sup>13</sup> states that small, deep, multiple cysts originate secondarily to amyloid changes in the blood vessels and cystic degeneration following splenic necrosis. Walls of these cysts may be of connective tissue if organization has taken place. Contents vary with age of cyst. Hematoidin and cholesterol crystals usually present in old cysts. Multiple cysts may be small or superficial or deep. Contents of old subcapsular hematomata may be gradually transformed into clear serous fluid.

Beneke<sup>13</sup> believes that small, multiple surface cysts originate from infoliation of peritoneal endothelium carried deep into the parenchyma when the splenic capsule is ruptured due to trauma. Small capsular tears permit fragments of splenic tissue to protrude, later these become sealed off and subsequently form cyst cavities. He states that cells lining these cysts and the peritoneal endothelium are identical.

Renggli<sup>13</sup> describes cysts lined with cuboidal epithelium and explains the presence of multiple deep cysts by a similar theory. Due to superficial inflammatory processes, portions of peritoneal endothelium are snared off which eventually are carried into the splenic substance and later, when stimulated to growth, form cysts lying deep in the parenchyma. A single layer of cuboidal epithelium lining these cysts is similar to that of the peritoneum, except that the latter is somewhat flatter due to pressure of neighboring or-



gans He states that these cysts originate in the embryo, where the endothelium of the peritoneum shows its original cuboidal character Otto<sup>13</sup> believes that this explanation holds only for small superficial cysts with a flat layer of cells not surrounded by splenic tissue

Pepere<sup>13</sup> points out that cellular nests may persist in the splenic capsule because of deviation of portions of the perisplenium during embryonic life Failure of these residues to disappear gives rise to serous cysts

**Case Report**—R Z, white, female, age 46, housewife, was first observed December 4, 1937 The patient had experienced a sensation of a "lump in chest," during the past three years, gradually increasing in intensity until the present time Recently she experienced dyspnea without exertion and noticed that her abdomen was protuberant Six months ago she felt a painless mass in the left upper quadrant of her abdomen No loss of weight, appetite good, no dyspepsia Appendix and one ovary removed 11 years previously Hemorrhoidectomy and vaginal plastic seven years ago Menses always regular until six months ago when she had three periods in July, she skipped August, and resumed normalcy again in September No history of trauma could be obtained

*Physical Examination* revealed a well nourished female, not acutely or chronically ill, no cyanosis or dyspnea Abdomen protuberant, with inversion of umbilicus Distended epigastric and lateral thoracic veins Flanks were resonant with dullness over a large mass, the size of a volley-ball, which was visible on inspection of left upper quadrant The tumor felt nodular and cystic and could be separated from the costal margin It did not move on palpation Extremities showed no large veins or edema Vaginal examination revealed no significant findings Hb 9.5 Gm, 58 per cent, R B C 3,300,000, W B C 7,100 Differential count showed no significant changes Wassermann reaction was negative

*Operation*—December 8, 1937 A ten-inch, left midrectus incision revealed an enormous mass, evidently the spleen, occupying the entire upper half of the abdomen and extending down below the umbilicus The peritoneal surface of the tumor was adherent to the entire dome of the diaphragm and to the posterior parietal peritoneum Although the adhesions were thick, they were easily separated and the spleen delivered from the abdominal cavity Adhesions to the sigmoid, pancreas and the splenic pedicle were doubly clamped, cut and ligated Recovery was uneventful The patient remained in the hospital 22 days

*Follow-Up*—January 12, 1938, six weeks postoperative General condition excellent, no masses palpable, liver not palpable and the operative wound is healed solidly throughout Blood count R B C 4,200,000, W B C 8,300, Hb 70 per cent June 21, 1938 Condition excellent, no loss of weight, no palpable masses in the abdomen Blood count R B C 4,100,000, W B C 8,700, Hb 70 per cent

*Pathologic Examination*—Dr Chester R Brown Specimen consists of an enormous spleen weighing 1,500 Gm, measuring 28.7×20×12.5 cm The spleen has been removed close to the entrance of the splenic artery and vein into the hilus There is no evidence of thrombi within these vessels Capsule is considerably thickened and in some areas is covered by dense, white patches firmly adherent to the underlying parenchyma Sagittal section reveals a very unusual appearance The spleen is surrounded, on one side, by a narrow border of apparently uninvolved parenchyma 4 cm in thickness, resembling normal splenic tissue This residual parenchyma consists of an admixture of solid tissue and cystic spaces The solid part is composed of numerous larger and smaller areas of friable tissue, yellow to brown in color, more or less completely surrounded by thin fibrous septa These masses vary in size from 1 to 2 cm to large nodular masses 8 to 10 cm in diameter There are four cystic areas varying in size and quite irregular in shape The two smaller areas are 6 to 12 cm in diameter and another, completely cystic, approximately 7.5 cm in diameter No distinct membrane lines these cavities Instead, irregular,

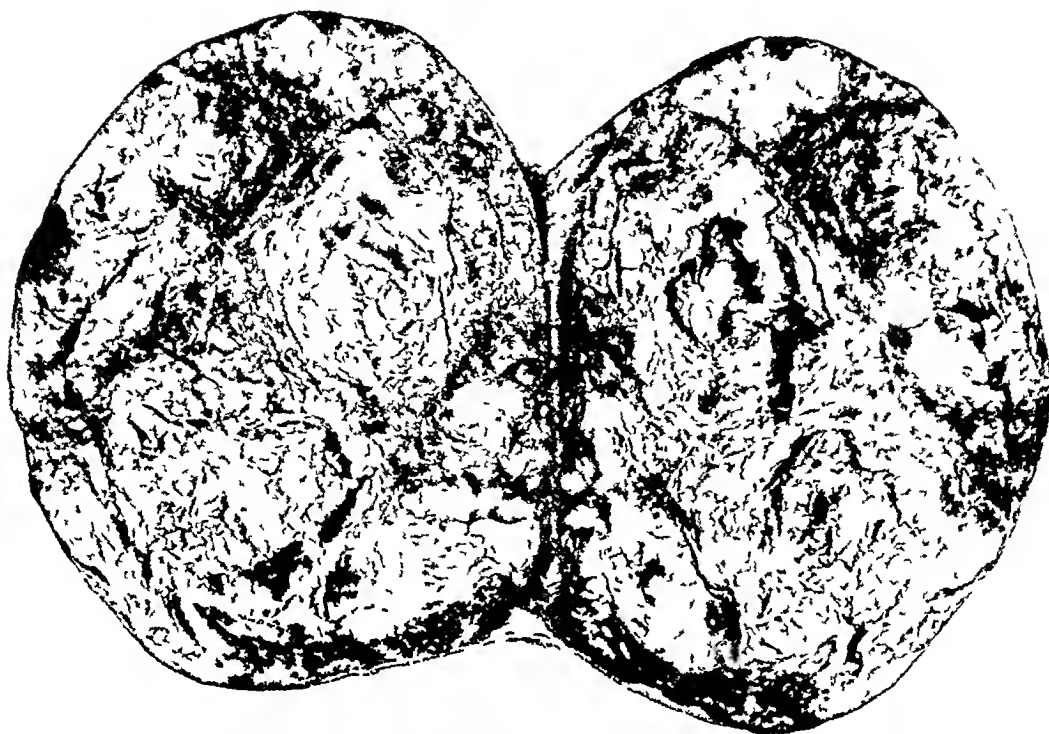


FIG 1—Photograph of the gross specimen. Note solid areas (dark) and various stages of cystic degeneration (light).

friable, nodular masses project into the lumen of the cysts from all sides, suggesting that the cavities had been formed by disintegration of parenchyma, previously solid (Fig 1).

*Microscopic Examination*—Sections of the capsule and pulp were stained with hematoxylin and eosin, mucicarmine, Mallory's phosphotungstic acid hematoxylin, Mallory's

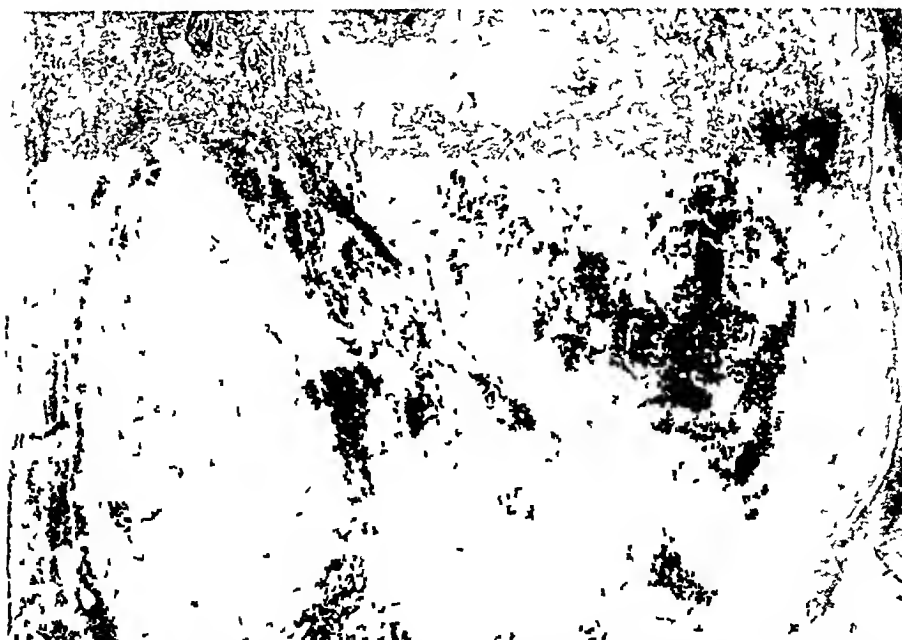


FIG 2—Photomicrograph of spleen taken near surface. At the left is residual parenchyma showing dilated lymph channels. The remainder of the pulp is entirely necrotic. (Low power).

aniline blue and potassium ferrocyanide. A section taken near the thickened capsule shows this to be composed of dense collagen fibrils. Immediately beneath this is a thin layer of residual splenic tissue, evidently the only remaining tissue which can be definitely recognized as a part of splenic pulp. This layer contains a few atrophic follicles, reticulum cells and fibrocytes with thickened trabeculae and a few dilated channels lined by a single layer of flat cells. Splenic sinuses are partially filled with red cells. Abundant collagen fibers lie within the thickened capsule and trabeculae and are condensed about the cystic areas forming more or less of a capsule. Beneath this layer, necrosis and cystic degeneration begin. Large areas of faintly pink-staining acellular material resembling coagulated

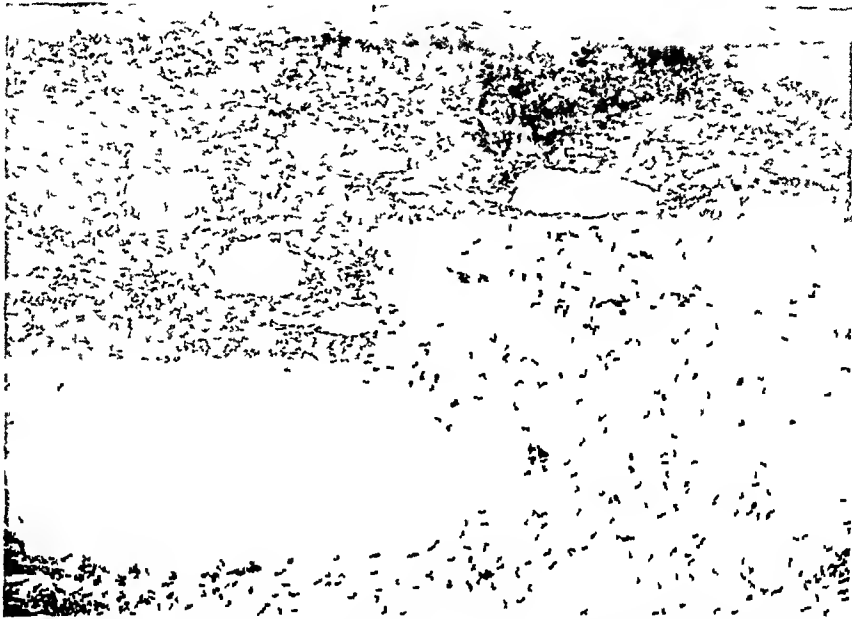


FIG 3 —Photomicrograph of residual parenchyma near cortex showing dilated lymph channels and compressed atrophic pulp (Low power)

serum and, in some areas, coagulated fibrin alternate with large extravasations of red cells not definitely in sinusoids. No endothelial lining is evident on the wall or within cystic spaces. Inflammatory cells are very rare. Portions of thickened trabeculae show dark-staining areas arranged in fibrillary strands. These give a positive iron reaction. Within the trabeculae are a few large congested blood vessels which show no thromboses, necrosis or amyloid degeneration. Mucicarmine stain failed to reveal the presence of mucus. *Pathologic Diagnosis* Multiple cystic disease of the spleen.

#### SUMMARY

The case history and pathologic details are given concerning an enormous cystic spleen which had apparently developed without evidence of abdominal trauma.

A short summary of the pertinent literature is included.

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# RHABDOMYOSARCOMA OF THE URINARY BLADDER

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CHICAGO, ILL

FROM THE TUMOR CLINIC AND THE DEPARTMENT OF PEDIATRICS (SARAH MORRIS HOSPITAL) OF THE  
MICHAEL REESE HOSPITAL CHICAGO ILL

RHABDOMYOSARCOMA arising from the musculature of the bladder is rarely seen. However, because of its grave prognosis and the difficulties encountered in treating it, this neoplasm is of special interest. The first case of malignant rhabdomyoma of the urinary bladder was that described by Monckeberg,<sup>25</sup> in 1907, occurring in a female, age 23. The tumor was resected, but recurred promptly and the patient died several months later. There were no metastases apparent. Another case was observed, in 1929, by Houette,<sup>14</sup> in a congenital diverticulum of the bladder in an infant, age 13 months. Montserrat and Garcia<sup>20</sup> reported a case in a male, age 43, in 1933. Partial resection of the bladder was performed but the patient died four months later, autopsy was not obtained. In 1936, Welfeld, Hill and Hillebrand<sup>42</sup> reported two cases in infants, both of whom died soon after treatment, with extensive local recurrence but no distant metastases. The only case of urinary bladder rhabdomyosarcoma with distant metastases was reported by Mackenzie and Chase,<sup>23</sup> in 1928, in a female, age 69. Autopsy showed a direct extension of the vesical neoplasm to the left ureter and distant metastases to the portal lymph nodes, liver and duodenum.

As far as we can ascertain from our search of the literature, the present case report constitutes the seventh instance of vesical rhabdomyosarcoma reported, and the fourth case to be observed in infants.

The histologically benign variant of this striated muscle tumor, the rhabdomyoma, has also been observed in the urinary bladder. The first case of this type was that of Cattani,<sup>3</sup> in a boy, age 12, reported in 1884. Vincenti,<sup>41</sup> Pavone<sup>29</sup> and Huesler<sup>15</sup> each added one case to the literature. Their patients were 13, 22 and seven years of age, respectively. In 1903, Benenati<sup>2</sup> assembled a group of 65 cases of rhabdomyoma, three of which occurred in the bladder. Shattock<sup>36</sup> described four specimens of this tumor from the Museum of the Royal College of Surgeons, in 1909. These all occurred in infants under two years of age. In 1924, Deming<sup>6</sup> reported a case of a histologically benign rhabdomyoma of the bladder in a 21 month old infant. This constitutes a total of 12 recorded cases of benign rhabdomyoma of the urinary bladder.

Because of the normal abundance of smooth muscle fibers in the muscular layers of the bladder wall, one might expect to find the leiomyoma and leiomyo-

sarcoma more frequently than the striated muscle tumor Keene and Tompkins<sup>18</sup> collected from the literature 59 cases of benign leiomyoma of the bladder Three cases of leiomyosarcoma of the urinary bladder have been reported, none of these exhibited distant metastases The cases of Powell<sup>30</sup> and Krauskopf<sup>19</sup> occurred in elderly individuals The case observed by Caylor and Walters<sup>4</sup> occurred in a four year old boy who died within two months following resection and irradiation of the bladder

*Pathogenesis*—There are a number of theories concerning the pathogenesis of striated muscle tumors of the urinary bladder Striated muscle fibers are found normally in the fetus, child and adult, around and often within the substance of the anterior part of the prostate, constituting the external vesical sphincter A more tenable hypothesis is the derivation of these tumors from cells of the myotome (anlage of the striated muscle of the abdominal wall) which have become displaced during the caudal growth of the wolffian duct to its vesico-urethral destination

*Pathology*—Grossly, the rhabdomyosarcomata of the bladder do not differ from the numerous other types of mesoblastic vesical tumors The growth frequently occurs in the form of grape-like masses suggesting hydatidiform mole Hence the descriptive name, sarcoma botryoides, applied to the rhabdomyoma of the cervix Usually, the tumor is of a white to grayish-yellow color, and has a fleshy consistency The surface is usually smooth and translucent Occasionally, glairy fluid can be expressed from the tissues on gentle pressure Usually, there is no ulceration of the bladder mucosa as the growth originates in the submucosa or intermuscular substance The space of Retzius is rapidly invaded, and following cystotomy or resection, the tumor usually grows luxuriantly to the abdominal wall, as happened in the present instance Distant metastases are rare, as has been pointed out

Histologically, the characteristic finding is a mesoblastic tissue composed predominantly of large cells with eosinophilic cytoplasm, containing longitudinal and transverse fibrillae These cells contain one to many large, oval, vesicular nuclei with deeply stained nucleoli The cells vary markedly in shape, size and staining quality, and mitotic figures are frequent

*Clinical Features*—The symptoms associated with the presence of this tumor are quite variable, but are not different from those of vesical sarcomata in general Occasionally, there are no associated genito-urinary symptoms, the only complaints being abdominal pain or the consciousness of an abdominal tumor Hematuria is rare, particularly as an initial symptom Descalopoulos,<sup>8</sup> in 1929, found hematuria as a symptom in only four out of 20 cases of bladder sarcoma in infants Due to the infiltration of the bladder neck and loss of bladder contractility, acute or partial retention of urine is a frequent occurrence Hence, the commonly associated symptoms of dribbling, enuresis, frequency, incomplete emptying of the bladder and dysuria The diagnosis is frequently made accidentally at exploratory operation for an abdominal tumor of undetermined nature In most of the reported cases of bladder sarcoma,

diagnosis has creditably been established before operation by cystoscopy or cystogram

*Prognosis*—The prognosis associated with rhabdomyosarcoma of the bladder is grave, as it is for all vesical sarcomata. None of the reported cases of rhabdomyosarcoma of the bladder have survived for more than a year following operative intervention. Most of the cases were treated by either cystotomy alone, cystotomy with partial resection of the bladder, sometimes followed by postoperative radiation, or cystotomy with cautery-fulguration of the tumor. The postoperative radiation administered has been in the form of roentgenotherapy, surface or interstitial application of radium element or radon. In our case, telecurietherapy with the four gram radium bomb was employed. The results have been uniformly bad. Rhabdomyosarcomata are usually radioresistant, as are most tumors in which an attempt is made to form a differentiated organ. Munwes<sup>27</sup> is the only author to present at all encouraging results in the treatment of vesical sarcoma. Three of his cases have remained well over five years, following radical operative treatment. In view of the fact that rhabdomyosarcomata rarely produce distant metastases, and that death usually occurs from cachexia and inanition associated with the exuberant growth of the local recurrence following incomplete surgical eradication of the disease, one is inclined to agree with Mintz,<sup>24</sup> who advocates total cystectomy, including resection of the urethra. In consideration of the definite, though slight and temporary, response to radiation observed in our case, telecurietherapy appears worthy of trial in advanced, inoperable cases.

*Case Report*—A N, male, age 10 months, was admitted to the Michael Reese Hospital, December 28, 1937. The child had been well until two months previously, at which time it commenced having severe pain on urination, as evidenced by an agonized facial expression and compression of the lower abdomen with its hands during attempts at micturition. Suprapubic cystotomy was performed elsewhere, and the parents were informed that the child was suffering from a malignant tumor of the bladder. Within one week following operation, a fungating mass had grown out to the anterior abdominal wall at the site of the cystotomy.

*Physical Examination*—The patient was markedly emaciated. The head exhibited a moderate hydrocephalus, the contour was brachycephalic, and a prominent ridge was palpable at the temporoparietal suture. The anterior fontanelle was widely patent. The skin of the back, chest and thighs was studded with café-au-lait spots. No skin tumors were visible. The suprapubic region presented a fungating mass, 12x6 cm in size, at the site of the previous suprapubic incision (Fig 1). Urine seeped constantly over the surface of this tumor. For the most part it was pink in color but in places was covered by a greenish-gray necrotic membrane. Biopsy suggested a malignant mesoblastic tumor apparently of neurogenic origin. Roentgenograms of the chest, skull and long bones showed no evidence of metastasis.

*Treatment*—Palliative treatment in the form of external radiation was instituted, and 1,000 mg-hr was administered daily on the four gram radium bomb at 10 cm distance, until 14,000 mg-hr had been given. The tumor diminished slightly in size during this two weeks' course of therapy, but the child had become so emaciated (its weight having dropped from 16 pounds, four ounces to ten pounds, twelve ounces) that radiation had

## RHABDOMYOSARCOMA OF BLADDER

to be discontinued. Its general condition grew steadily worse, the tumor increased again in size, and the child died, four weeks after treatment had been stopped.

*Autopsy*—There was a marked external hydrocephalus. The skin of the back, chest and thighs presented many cafe-au-lait spots varying in size from 0.5 to 2 cm. in diameter. The suprapubic region of the abdominal wall was covered by a fungating, pinkish-gray mass 15x12x6 cm. in its greatest dimensions. The surface of the tumor was moist and granular. On cutting through the abdominal wall one found that the tumor arose from the outer coats of the bladder wall. The space of Retzius was completely filled by tumor. The mucosa was smooth and apparently not involved. Both ureters were moderately dilated.



FIG. 1.—Showing the rhabdomyosarcoma of the urinary bladder with extension to abdominal wall.

*Pathologic Examination*—In a section of the bladder wall near the mucosa, a few alveolar-like structures were seen to lie in a dense stroma and were composed of transitional epithelial cells isolated from the surrounding tissue by a well formed basement membrane. The stroma was cellular and contained various types of cells. Many of the nuclei were oval in form and appeared to have no surrounding cytoplasm. Others, and this type predominated, consisted of elongated dark-staining nuclei from whose poles fibers were seen to emanate. In another area, large nuclei were arranged in circular form surrounded by pink-staining material. Occasionally, large fibers with peripherally placed nuclei were seen. Cross and longitudinal striations were noted in fibers which were quite variable in size. A moderate number of mitotic figures were seen throughout the section. *Histologic Diagnosis* Rhabdomyosarcoma of the urinary bladder.

*COMMENT*—This was a malignant, striated muscle cell tumor arising from the wall of the urinary bladder in a male infant age 10 months, which extended to the abdominal wall following cystotomy and in a short time attained the size indicated in Figure 1. Because of the emaciated condition of the child, the extensiveness of the bladder tumor, and the possibility of a tuberous sclerosis associated with the pigmentation suggesting von Recklinghausen's disease (neither being found at autopsy), operation was deemed inadvisable. Palliative radiation was administered by telecurietherapy (radium bomb) with the result that the tumor began to react locally and shrink.



in size. Because of the marked weight loss which occurred, such radiotherapy had to be discontinued after two weeks.

At autopsy, the only findings of significance, besides the bladder tumor, were the café-au-lait spots and the external hydrocephalus. The authors wish to call attention to the frequent association of café-au-lait spots (as observed in this and other recent cases) with tuberous sclerosis, glioma of the brain and benign or malignant mesothelial tumors, including those of the genito-urinary tract.

*Discussion*—In connection with our study of the striated muscle cell neoplasms of the urinary bladder, it appeared of interest to investigate the occurrence of such tumors in other parts of the body. The earliest record of a striated muscle tumor is apparently the case of Rokitsansky,<sup>33</sup> reported in 1849.

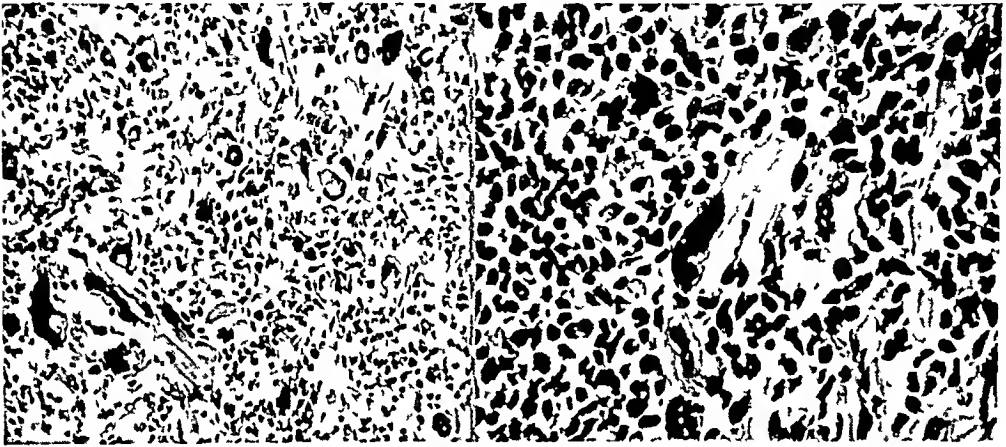


FIG. 2—Photomicrograph of the rhabdomyosarcoma of the urinary bladder, a few fibers with longitudinal and cross striations are to be seen.

FIG. 3—Photomicrograph of the rhabdomyosarcoma of the urinary bladder (High power).

This was a paratesticular tumor, in a boy, age 18, composed of striated muscle and presumably arising from the gubernaculum testis. Benenati,<sup>2</sup> in 1903, collected 65 cases of rhabdomyoma. Over one-half of these were located in various portions of the genito-urinary tract. Most of these cases occurred in the first or second decade of life. Only one of Benenati's cases exhibited malignant characteristics histologically or clinically. This case was a tumor arising from the muscles of the thigh with widespread metastases.

Malignant rhabdomyoblastomata occur in the skeletal musculature somewhat more frequently than in the genito-urinary system. Charache,<sup>5</sup> in 1936, collected 11 cases from the literature. In most of these, the tumor followed severe trauma, in contrast to the genito-urinary rhabdomyoblastoma which is usually thought to be the product of disturbed embryologic development. These tumors occurred in older individuals and metastasized more frequently than the genito-urinary tumors of similar histologic nature. Charache's case exhibited metastases to lungs, liver, kidneys and local lymph nodes. Rakov<sup>31</sup> has recently written a most comprehensive summary of this condition, which was diagnosed in 15 cases at the Oncological Institute in Leningrad.

This variety of tumor is encountered even more frequently in the cardiac musculature. Reeves and Michael<sup>32</sup> mentioned the existence of 45 cases of rhabdomyoma of the heart and reported an additional case of their own. The condition is especially prone to occur in infants with cerebral sclerosis. Of 12 cases of cerebral sclerosis observed by Wolbach,<sup>43</sup> six had rhabdomyoma or rhabdomyosarcoma of the heart.

Both benign and malignant varieties of this striated muscle neoplasm have been found throughout the genito-urinary tract. According to Bell,<sup>1</sup> leiomyomata, rhabdomyomata, fibromata and neurofibromata are not infrequently encountered in association with tuberous sclerosis. On the other hand, Kass<sup>16</sup> maintains that there are but five authentic cases of neurofibromatosis of the bladder in association with von Recklinghausen's disease, and that his case constitutes the only reported case of this condition occurring in childhood.

While the so-called Wilms' tumor of the kidney is usually an adenosarcoma histologically, it not infrequently shows foci of adult or undifferentiated embryonal striated muscle and at times is a pure rhabdomyosarcoma.

Some ten cases of rhabdomyosarcoma of the prostate have been reported. Greig's<sup>11</sup> case and that of Katzmänn<sup>17</sup> occurred in early childhood. The cases of Ewing,<sup>9</sup> DeRom and Thomas,<sup>7</sup> Kretschmer<sup>20</sup> and of Foucar<sup>10</sup> were all in young adults. Metastases were observed only in the cases of Squier<sup>38</sup> and Foucar.

The literature on rhabdomyosarcoma of the testis is somewhat confusing, because of a tendency to classify as rhabdomyosarcomata tumors which are actually teratomata containing foci of striated muscle. Most of the pure striated muscle cell tumors of the testis have occurred in children or young adults. Neumann's<sup>28</sup> case was a rhabdomyoma in a child, age 3½ years. Schamschin's<sup>34</sup> case was the malignant variant of this neoplasm and occurred in a child, age 4. Ssinelscikowa<sup>39</sup> reported a case in a boy, age 15, with mediastinal, pulmonary and diffuse intra-abdominal metastases. One of us (Uhlmann) has personally observed a case of rhabdomyosarcoma of the testis in a male, age 22, who exhibited retroperitoneal lymph node metastases at death, which occurred two years after the onset of the condition. Rhabdomyosarcoma of the spermatic cord has been observed in young males by Hirsch,<sup>12</sup> Monckeberg<sup>25</sup> and Stoercke,<sup>40</sup> the latter's case being accompanied by diffuse metastases.

Sporadic cases of rhabdomyosarcoma of the corpus uteri have been found in elderly women by Lochrane,<sup>21</sup> Shaw<sup>37</sup> and Shapiro.<sup>35</sup> The occurrence of striated muscle tumors in the uterus is difficult to explain. It has been suggested that the displacement of embryonic mesodermal cells from the myotome of the dorsal region must occur during the caudal growth of the wolffian duct toward its vesico-urethral anlage. This would account for the occurrence of striated muscle cell neoplasms not only in the uterus, but in the cervix and vagina as well.

The vulvar orifice in children is apparently one of the more common locations for this neoplasm. Holmes,<sup>13</sup> in 1906, compiled 39 cases of rhabdo-

myosarcoma of the vulva, and several cases have been reported since Lockwood's<sup>22</sup> case developed generalized intra-abdominal metastases

#### SUMMARY AND CONCLUSIONS

In conjunction with the report of a personally observed case of rhabdomyosarcoma of the urinary bladder in an infant, age 10 months, the authors have reviewed the pathogenesis, clinical features, histologic characteristics and prognosis of this rarely observed tumor

The occurrence of benign rhabdomyoma of the bladder is mentioned, and the frequency of rhabdomyosarcomata in other organs of the body is reviewed

Total cystectomy, including resection of the urethra, is recommended as the treatment of choice in operable cases. In advanced cases, telecurietherapy appears worthy of trial, especially since distant metastases are rarely observed in this condition

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## FURTHER OBSERVATIONS ON BENIGN TUMORS OF THE TENDON SHEATH

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FURTHER observations as to the histogenesis of benign tumors of the tendon sheath and the opportunity of investigating 23 more cases of such tumors led us to make this report

From a review of the recent literature, it appears that the question of whether this type of tumor is a true neoplasm or merely a granuloma is still a matter of much dispute Sprenger<sup>1</sup> considers the tumors of the tendon sheath as xanthomatous giant cell granulomata, since he believes them to be traumatically conditioned, chronically inflamed resorptive tumors Lecene and Moulouguet<sup>2</sup> do not include these tumors among the neoplasms, showing their dystrophic origin Berti<sup>3</sup> states that the tendon sheath tumors are pure and simple granulomata, obscure with respect to their etiology and pathogenesis, but sufficiently clear to permit their classification as previously mentioned In the opinion of Bloodgood,<sup>4</sup> they are real granulation tissue and often of the xanthoma type

On the other hand, Gorog,<sup>5</sup> Torchiana,<sup>6</sup> Durante,<sup>7</sup> Tomiselli,<sup>8</sup> Katsurashima,<sup>9</sup> Spiess,<sup>10</sup> King,<sup>11</sup> Faulkner,<sup>12</sup> Beckman,<sup>13</sup> Albertini,<sup>14</sup> Mathews,<sup>15</sup> Cooperman,<sup>16</sup> Aguilar,<sup>17</sup> Vermooten,<sup>18</sup> Bellamy,<sup>19</sup> Krogins,<sup>20</sup> Lewis,<sup>21</sup> and Geschickter and Lewis<sup>22</sup> consider these tumors to be true neoplasms Although the terminology differ with the various authors, the terms xanthosarcoma, myeloplax tumors, giant cell sarcoma, myeloid endotheliomata, and myeloxanthomata are being used

Authors who regard these tumors as neoplasms do not consider the presence of blood and cholesterol as primary but as a secondary factor, since these tumors are, due to their position in growth, easily subject to trauma

*Material Considered*—We have clinical data on 14 of 23 cases, have summarized the clinical course in Table I The specimens of the other nine cases were sent in to the laboratory from the outside, without any accompanying clinical data

*Age Incidence and Site of Tumor*—The tumors occurred in individuals between the ages of eight and 70, all but five patients being between the third and fifth decade of life In 11 cases, the tumors were situated on the hand, eight cases having them on the right hand, involving the index finger in two, the third finger in four, and the fourth finger in two instances Three cases were located on the left hand In two instances the tumor was

# TUMORS OF THE TENDON SHEATH

TABLE I  
SUMMARY OF 14 CASES OF BENIGN GIANT CELL TUMORS OF THE TENDON SHEATHS

No	Age	Sex	Race	Location	Recur- rences	Size in Cm	History of Trauma	Dura- tion	Comment
1	40	F	C	Prox phal rt ring finger	0	1.0 x 0.7 x 0.9	No	12 mos	—
2	9	F	C	Second phal rt third finger	0	0.5 x 0.7 x 0.4	No	12 mos	Pain on pressure
3	31	F	W	Rt index finger	1	1.5 x 1.5 x 0.8	No	24 mos	Pain occasionally
4	70	M	W	Rt ankle	0	2.5 x 1.8 x 2.5	Yes	18 mos	Pain occasionally
5	13	M	C	Second phal rt third finger	0	2.0 x 2.0 x 1.0	No	18 mos	—
6	13	M	W	Rt lat bord sole rt foot	1	1.5 x 1.5 x 1.0	No	24 mos	—
7	46	F	C	Second phal rt third finger	0	3.5 x 7.3 x 1.5	No	48 mos	—
8	30	F	W	Radial side rt ring finger	0	1.3 x 1.0 x 0.6	No	12 mos	—
9	45	M	W	Rt palmar surface opposite third finger at metacarpal phalangeal joint	0	1.3 x 1.3 x 0.5	Yes	9 mos	Pain in palm
10	8	F	W	Second phal rt index finger	0	1.5 x 1.5 x 0.8	No	14 mos	Pain on pressure
11	28	F	W	Second phal L fifth finger	0	1.2 x 0.9 x 1.5	Yes	24 mos	Pain on pressure
12	50	F	W	Prox phal 1 ring finger	0	1.2 x 1.2 x 0.7	—	—	—
13	—	M	W	Back of neck at sixth cerv vertebra	2	5.5 x 3.7 x 3.5	No	6 mos	—
14	—	M	—	L ring finger	0	—	—	36 mos	—

Cases Nos 15 to 23, inclusive, had no accompanying clinical data

situated on the fourth finger, and in one instance on the fifth finger. In the remaining three cases, one tumor was found on the back of the neck at the level of the sixth cervical vertebra and evidently arising from the aponeurotic sheath of some of the deep muscles of the back. The second arose from the fascial sheaths about the ankle, and the third arose from the lateral border of the sole of the right foot.

*Duration*—The duration of time between the detection of the growth and the administration of medical attention varied from nine months to four years, and in one case pain was present for three weeks before the patient sought medical aid. Only three cases gave a history of trauma, one occurred 14 months, the second 18 months, and the third two weeks before the tumor growth was apparent to the patient.

*Incidence of Recurrence*—Recurrence occurred in three cases, the tumor in the first case returning about five months after operation, the second, five years after the first and one year after the second operation, and the third, 10 years after the first operation.

*Sex*—Ten of the 23 cases mentioned were females and eight males. Unfortunately, there are no clinical data available on the remaining five cases.

*Pathologic Examination*—*Gross* The size of the tumors was determined in 13 cases, the largest being that of the neck, measuring  $5.5 \times 3.7 \times 3.5$  cm., and the smallest being that of the second phalanx of the right third finger, measuring  $0.5 \times 0.7 \times 0.4$  cm. The tumors were found to be firm, lobulated, and cauliflower-like in appearance, and having numerous fibrous tags. The sectioned surfaces were grayish-white in color and streaked with areas of darker gray. Some areas of these tumors were tinged canary-yellow to yellowish-brown.

*Microscopically*, all the tumors stained with hemalum and eosin were found to contain type cells which were characterized by their polygonal or oval shape. The nuclei were of moderate size, round, oval, or slightly elongated, frequently somewhat indented, and with fine or occasionally coarse granules of chromatin. The cytoplasm was sparse. The type cells which tended to line the crevices contained a little more cytoplasm, except in two cases, where the desmoplastic change was so marked that the cells were elongated and had protoplasmic processes with a suggestion of fine fibrils extending from the cellular membranes. The nuclei here were also elongated and had coarse chromatin granules scattered throughout. With the exception of one, all the tumors had cleft formations, and in that one exception, there was a suggestion of the clefts. In areas where the type cells were separated from each other by connective tissue, it was found that the nuclei were elongated and had no apparent cytoplasmic membrane. In some of the tumors, and especially in that situated on the neck, there was definite evidence of transition of the type cell from the polygonal shape to the fibroblastic type.

Giant cells were found to be present in every case. They were characterized by being fairly well defined and containing a homogeneous and slightly eosinophilic stained cytoplasm, with nuclei which numbered five to 50, and

in two cases, where the cellular elements were quite proliferative, 50 to 100 nuclei were found per cell. These nuclei were regular, slightly oval or round, and had a fine, deeply stained chromatin network. Many of these giant cells were found in the crevices lined by the type cell.

Iron pigment, xanthoma cells and histiocytes laden with iron pigment were found in only seven cases of this series. These elements were found to be closely related. The xanthoma cells, the iron pigment, and the pigment-laden histiocytes were usually situated near a blood vessel, indicating that at one time hemorrhage occurred, and with the disintegration of the red blood corpuscles, the hemosiderin and cholesterol deposits were invaded by the histiocytic elements of the body. In five tumors, the capsule was partly formed by a thick layer of xanthoma cells in which iron pigment was found. In six instances of the above seven cases, giant cells were found close to the iron pigment, and they were characterized by peripherally placed, round, pale-stained nuclei with a pale-stained cytoplasm closely resembling the foreign body giant cell.

All of the tumors had capsules of loose to dense connective tissue which projected into the tumor mass and split up, as it went along, into fine coarse fibrillar strands which acted as a supporting network for the type cells. Hyalinization of the connective tissue was found in some instances, especially towards the center of the tumor tissue.

The blood vessels in the tumor masses were few and thin-walled. The endothelium was flattened. In the capsule of the tumors, however, some of the vessels had thickened walls, and the endothelium was swollen.

*Discussion*—In view of the present study of these cases, and comparing them with the various theories offered on the histogenesis of benign tumors of the tendon sheath, we are more inclined to consider these tumors as true neoplasms and of mesothelial origin, for the following reasons. Throughout this entire series of cases, there are type cells which are characterized by round, oval, polygonal, or at times elongated shapes, with a somewhat distinct and slightly eosinophilic cytoplasm and containing a round, oval or slightly elongated nucleus which is often indented. These cells, in every case but one, which offers but a faint suggestion, show a definite tendency to line clefts which, in a way, imitate the arrangement of synovial cells in a normal tendon sheath surrounding a tendon (Fig 1). King<sup>11</sup> stresses the fact that synovial membranes have a characteristically histologic picture, and that tendon sheath tumors may be interpreted in terms of this normal cellular structure. This impressed him with the fact that the synovial spaces in tumor tissue and not the giant cells or xanthoma cells are an important and characteristic feature of this tumor. He concludes, therefore, that tumors of tendon sheaths arise from the cells of the synovial membrane of the sheath, and the morphology and nature of the growth depend upon the potentialities of the originating cells.

In other instances, where the type cell is individually separated by connective tissue, the cells are found to be elongated, frequently have apparent



protoplasmic projections of the cytoplasm, and occasionally fibrils. The nuclei are elongated with fine chromatin network. This is especially noted

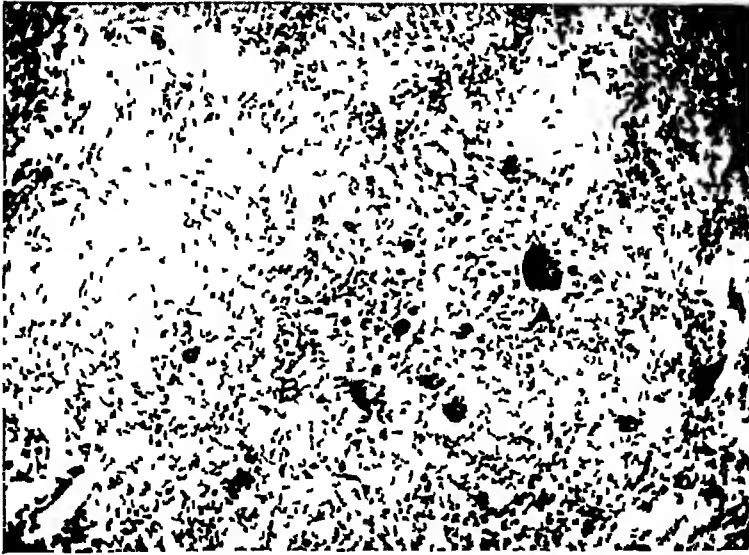


FIG 1—Photomicrograph illustrating the giant cell (A) and the crevices (B). These crevices may be considered as cracks in the tissue but are not so since they are seen persistently in all tumors of this type and are quite regular in shape and are always lined by a single row of epithelial like cells ( $\times 150$ ).

in three of our cases. In two cases, there was active proliferation and a few mitotic figures were found, the tumor cells as a whole took on the appearance of proliferating fibroblasts with elongated nuclei containing nucleoli

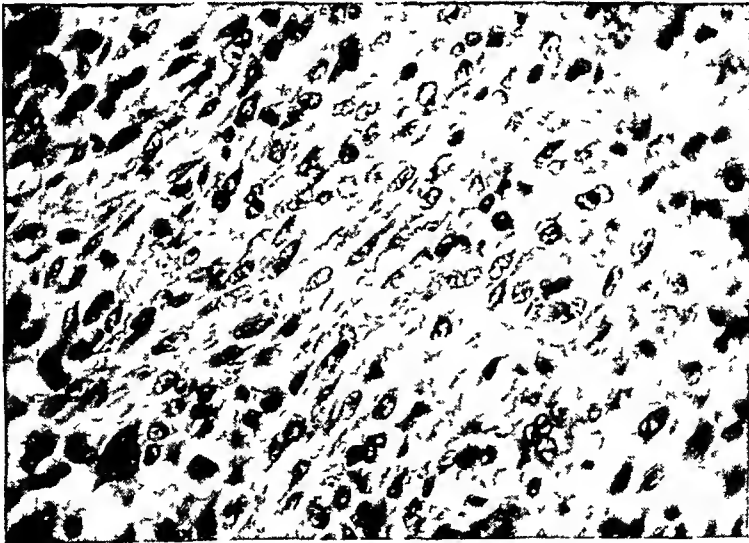


FIG 2—Photomicrograph illustrating the tendency of the type cell to become fusiform and fibroblastic in nature ( $\times 600$ ).

(Fig 2) In two cases, particularly that of the tumor on the back of the neck, the type cell seemed to show transitional forms taking on the appearance of the swollen, elongated, fibrillar, connective tissue cell with a swollen

and elongated to oval nucleus. In the more dense portions of the connective tissue of this tumor, the cells became elongated and showed formations of extracellular fibrillar connective tissue. The above described finding may be a factor in the great amount of connective tissue usually found in these tumors.

This is substantiated by Vaubel,<sup>23</sup> who, in his work on the growth of synovial tissue culture, has shown that under low nutritive value of the media, the synovial cells remained the same for about 60 days, provided transplants of the growth to new media were made every 10 days. After 60 days, it was not often possible to prevent transformation into a growth having a fibroblastic character. The cells in their transformation became small and spindle-shaped, with numerous long, sharp, fine processes, and contained smaller and less clearly demarcated nuclei. The highly refractile granules of the synovial cells became smaller and less distinct and disappeared in the next transplant. Generally, the fibroblastic appearance, once formed, tended to remain. In transplants with greater nutritive value media, the fibroblastic changes occurred more readily.

Maximow<sup>24</sup> has also shown that in tissue cultures made of peritoneal exudate, mesothelial cells are transformed into fibroblasts. Key,<sup>25</sup> in his experiments on rabbits, has shown that after performing a complete hemisynovectomy on knees of rabbits, and studying them at regular intervals of two days for the first 22 days, and later six to 18 days apart, up to 104 days after the operation, the joint was again approximately normal, 60 days after the hemisynovectomy. The new synovial membrane was formed *in situ* by the metaplasia of the underlying connective tissue cells, and there was little or no tendency of the surface growths at the edges of the normal synovia to cover the denuded area, as there is in the repair of a defect in an epithelial surface. He believes that the synovial cells are connective tissue cells, slightly specialized by their location on a free connective tissue surface.

This experimental finding is simulated very closely in two of our tumors, in which the clefts are lined by elongated cells having a suggestion of protoplasmic processes with fine fibrils. Murphy,<sup>26</sup> in his work on the ankylosis arthroplasty of the hip joint, has shown the formation of a new synovial space by the interposition of muscle aponeurosis, with the formation of a definite lining membrane.

Similarly, in the malignant form of tumors of the synovial tissue, described by Smith<sup>27</sup> as a synovioma, the tumor is characterized by spaces lined in many instances by low cuboidal epithelial-like cells separated by compact cords of spindle-shaped cells which, in some portions of the tumor mass, are devoid of intercellular substances and fibrils. Mitotic figures are present in both types of cells. He believes that both are derived from a common multipotential cell, since he has shown the synovial lining type and the supporting stromal type with intermediate forms of cells between the two.

In previous observations, made by one of us<sup>28</sup> (A. B. R.), we were impressed in one case by the presence of giant cells in the tumor and their close

topographic relation to old hemorrhagic areas, and the absence, in the second case, of giant cells where recent hemorrhages and old hemorrhagic areas were absent. At that time, the findings led one to consider them giant cells of endothelial origin with a tendency to organize the hematoma. But with the study of additional material in 23 different cases, it was found necessary to withdraw the previous view, and now consider them as part of the ground substance of the tumor mass, for the following reason. In all of the 23 cases, with the exception of one case reviewed in this series, there were giant cells closely related to the type cell, and in seven of these 23 instances, there were found hemorrhage, iron pigment, xanthoma cells or iron pigment-laden histiocytes. Where the iron pigment and xanthoma cells were found, the giant cells were not closely related to these foreign elements but were closely related to areas where the type cell was found. In six cases, there were apparently two types of giant cells, one resembling the foreign body giant cell with peripherally placed pale-stained nuclei closely related to the iron pigment and xanthomatous cells, and the other type having centrally placed nuclei which resembled the nuclei of the type cell and was closely related to the group of tumor cells proper.

This present view agrees with that of Albertini,<sup>14</sup> who considers the giant cells to be derived from mesenchyme and states that they are the same substance as the ground cells except that their protoplasm has failed to undergo division.

Stewart and Flint<sup>20</sup> have also shown giant cells to be present in the absence of cholesterol deposits. They, however, believe the giant cells to be endothelial in origin.

Other investigators (Fleissig,<sup>30</sup> and Spieniger<sup>1</sup>) believe these cells to be foreign body giant cells, due to the presence of extracellular cholesterol and their ester deposits. Goring,<sup>5</sup> on the other hand, assumes that the giant cell is part of the ground substance, since, in these tumors, it develops at a remote distance from the cholesterol deposits and in contrast to the true foreign body giant cell which, as a rule, develops immediately around the foreign particle.

Mallory<sup>31</sup> states that at least two different types of giant cells occur in tumors. The true type arises from multiple mitoses and appears in a great variety of rapidly growing tumors, such as the fibrosarcoma or glioblastoma. It does not differ essentially from the other cells of the tumor, except in size. The other, the foreign body giant cell, is formed most commonly in new growths involving bone and occurs in both rapid and slow growing tumors. It is due to endothelial leukocytes invading tumors and fusing to form giant cells. In none of our tumors was there bone involvement, and upon close examination, the nuclear structures of the giant cell in these cases are identical with those found in the type cell.

Although some of the observers, as McWhorter and Weeks,<sup>32</sup> are under the impression that these tumors are due to a systemic disturbance of cholesterol metabolism, as in multiple xanthoma, one should still consider cholesterol deposits as secondary manifestations, undoubtedly due to trauma since the xanthoma cells are found in close relation to areas of trauma, as in-

licated by old hemorrhage with liberation of iron pigment and cholesterol by the degenerated red blood cells

In seven of our cases, where iron pigment was found, xanthoma cells were usually present, and then around a blood vessel, whereas, in the other cases, where no hemorrhage was found, cholesterol deposits, iron pigments and lipophages were absent. In one case a recent hemorrhage was present with absence of xanthoma cells and cholesterol deposits.

Unfortunately, we were able to obtain only one blood cholesterol determination, and that of a case where the tumor had recurred a second time. The blood cholesterol was 148 mg per 100 cc, which is quite within normal limits.

Gorog,<sup>5</sup> and Aguilar<sup>17</sup> have also reported normal blood cholesterols in patients suffering from tendon sheath tumors. Furthermore, it has been shown by Stewart,<sup>33</sup> that deposits of cholesterol may occur in various pathologic lesions, one of which is due principally to local tissue changes with no chance for escape of the products of disintegration.

Katsurashima<sup>9</sup> believes that the xanthomatous tissue in question probably developed secondarily in the tumor as a partial manifestation of a constitutionally conditioned hypercholesteremia.

As for the iron pigment, its close topographic relationship to blood vessels indicates that it, like the cholesterol deposits, is derived from degenerating red blood cells. The pigment is readily engulfed by numerous histiocytes.

One more interesting phase is the subject of recurrences. In three cases where there were histories of recurrences, two were not heard from after the second removal of the tumor from the finger, and the other had a second recurrence following a removal 14 months previous. This can easily be explained by the fact that complete extirpation of the tumor was not effected at the second operation. In addition, there was no evidence of metastasis to lymph nodes situated nearby, nor did the patient show constitutional signs of a long standing malignancy.

It seems appropriate, therefore, to consider these growths relatively benign, and if a complete surgical removal is performed, they do not recur. Radical surgery in tumors of this kind is not indicated.

In view of the study of the present material, the giant cells are to be considered as part of the ground substance of the tumor tissue, and this, necessarily, changes the descriptive terminology of the tumor mass from benign tumors to benign giant cell tumors of the tendon sheath.

#### CONCLUSIONS

- (1) Benign giant cell tumors of the tendon sheath are true neoplasms.
- (2) Cholesterol and iron pigment deposits are secondary to the tumor growth and are liberated by the degeneration of the red blood cells.
- (3) Xanthoma cells are formed only in the presence of iron and cholesterol deposits.
- (4) Giant cells are mesenchymal in origin and are part of the ground substance of the benign cell tumor of the tendon sheath.

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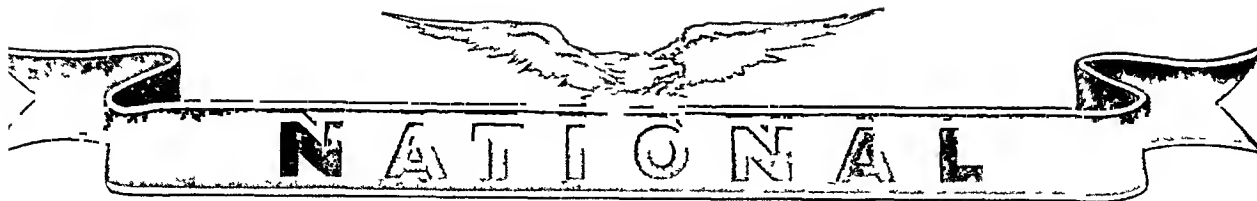
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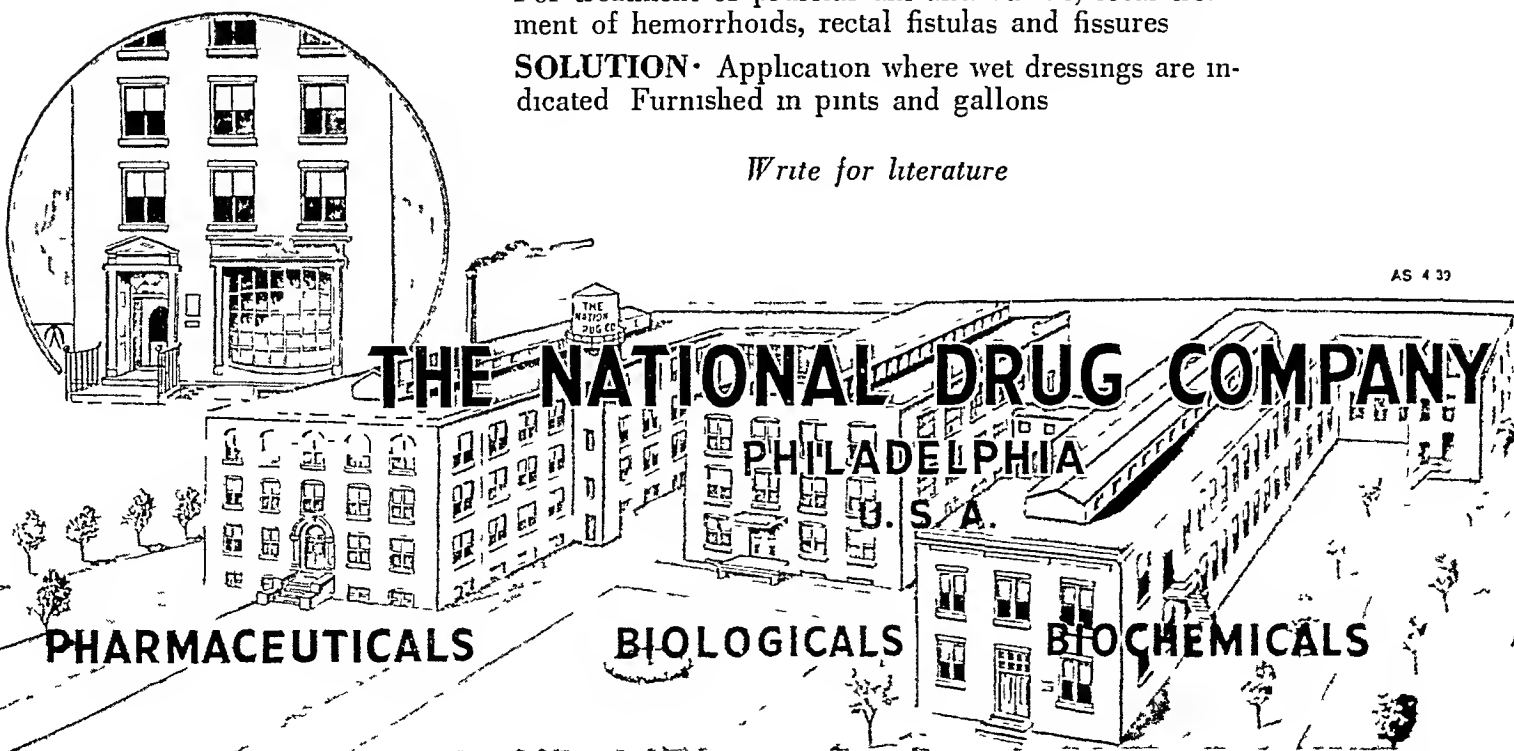
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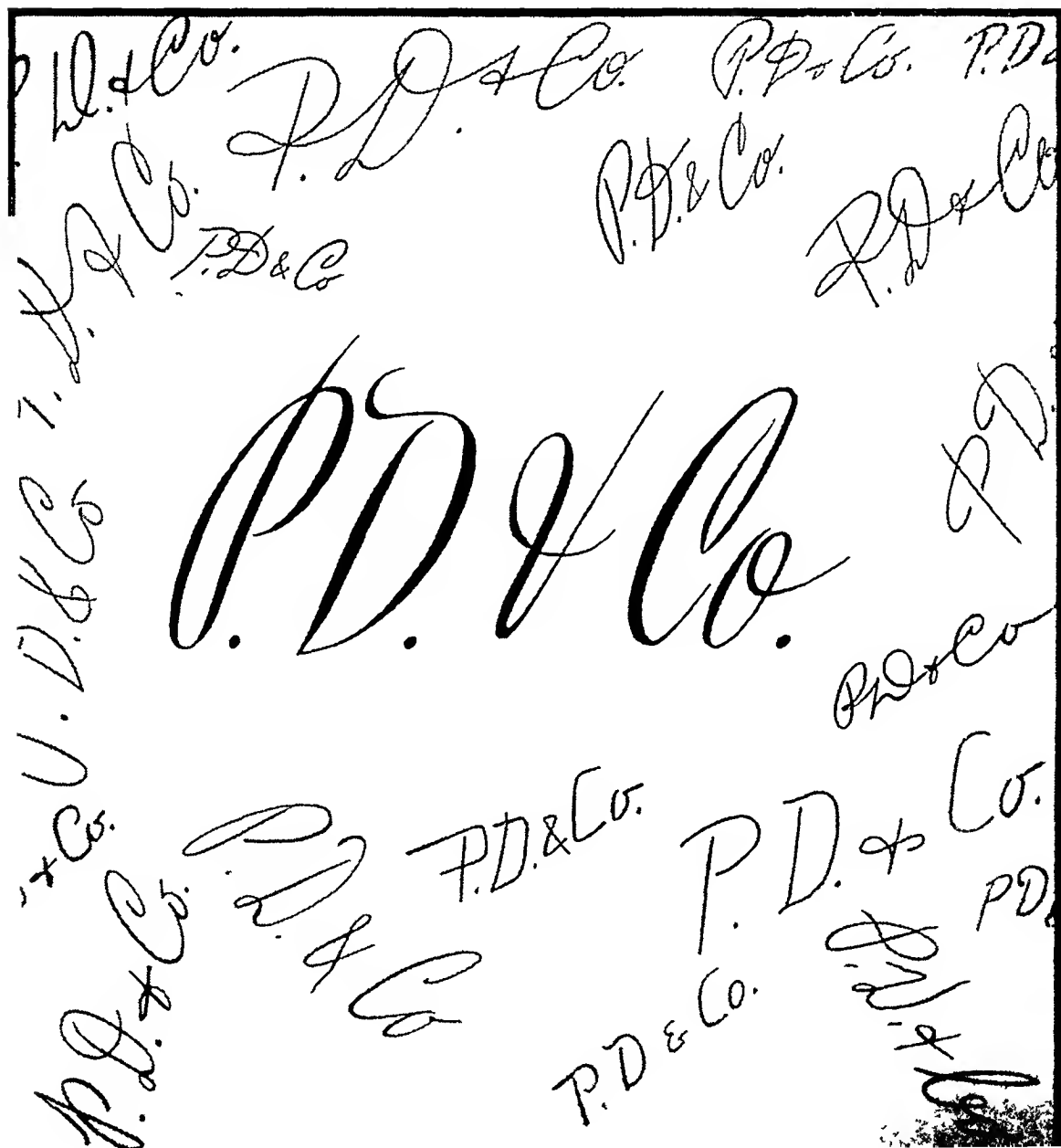
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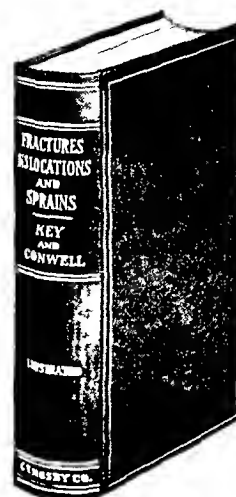
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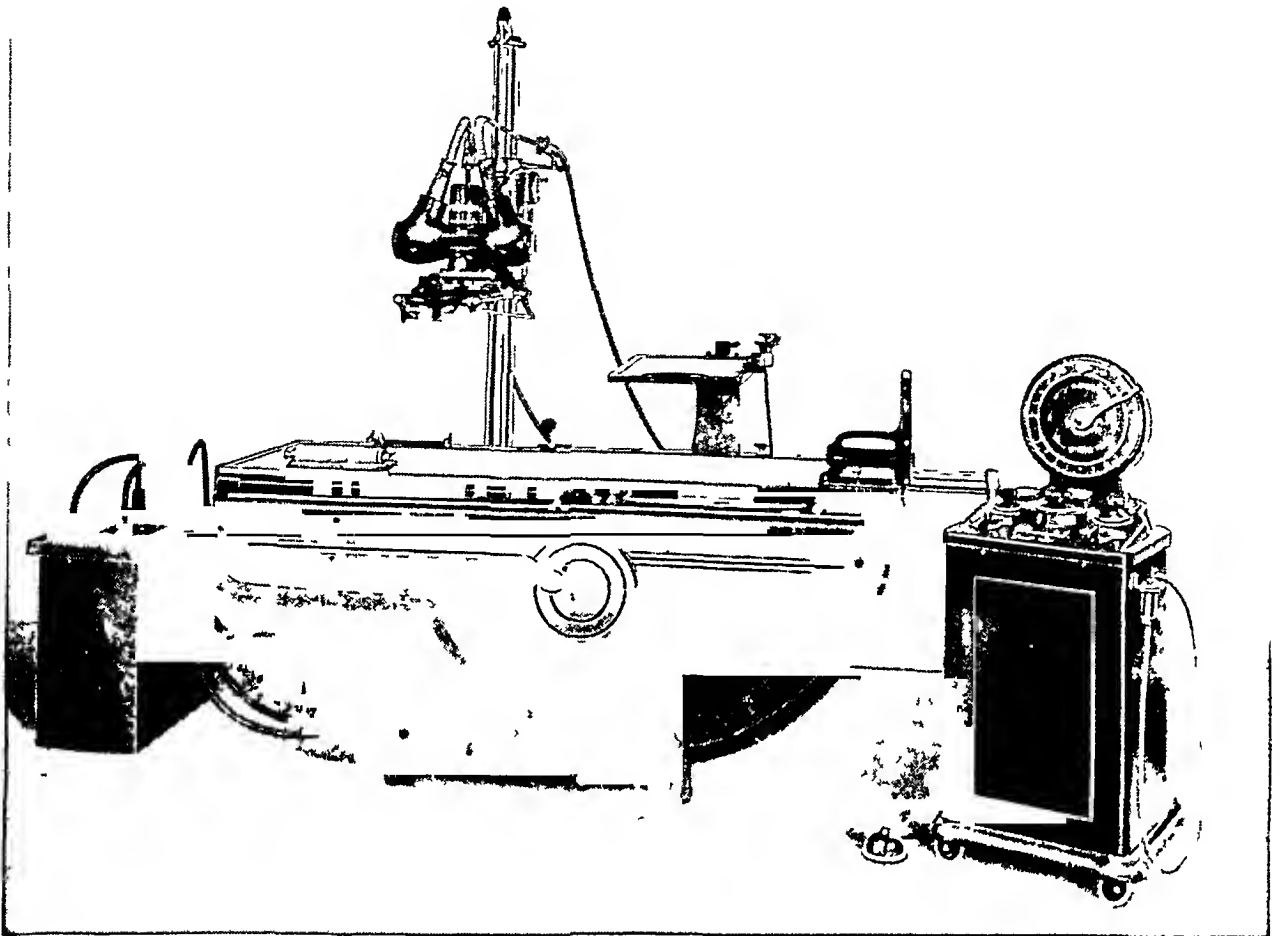
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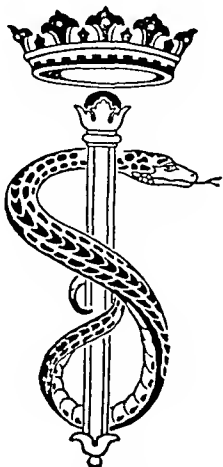
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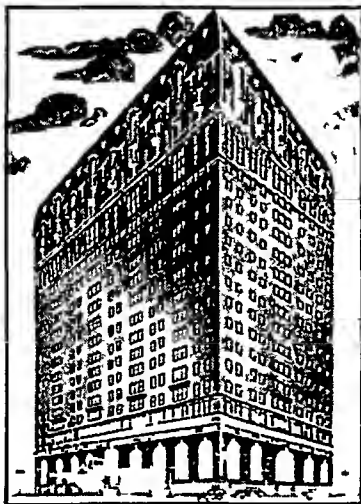
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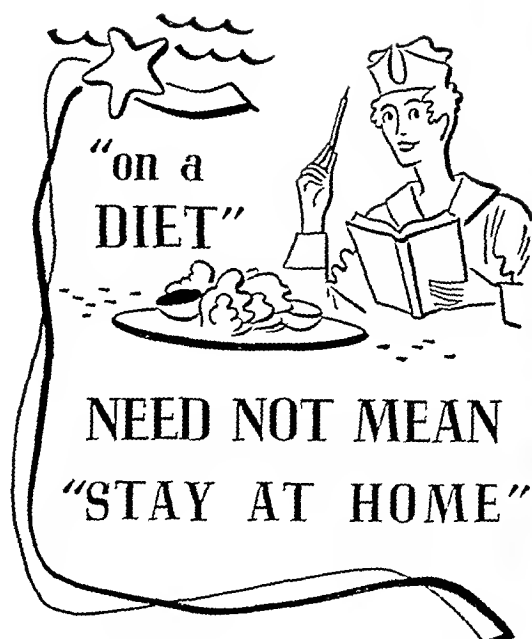
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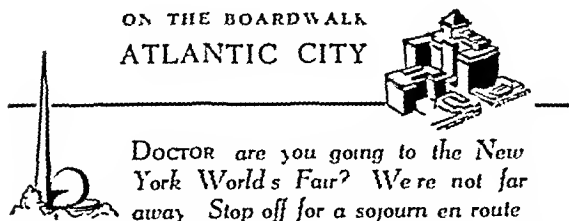


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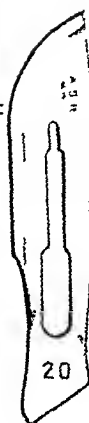
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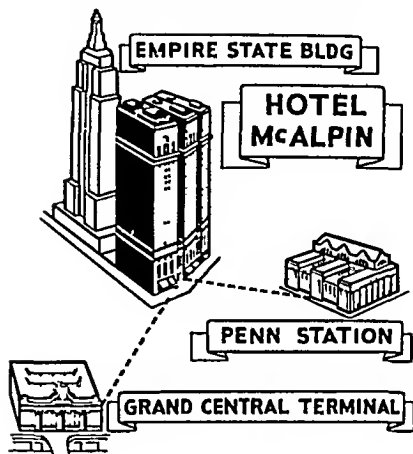
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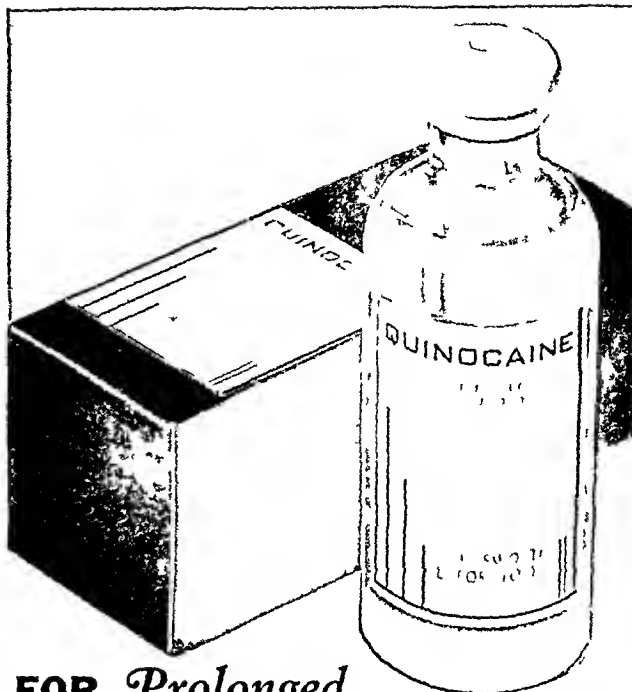
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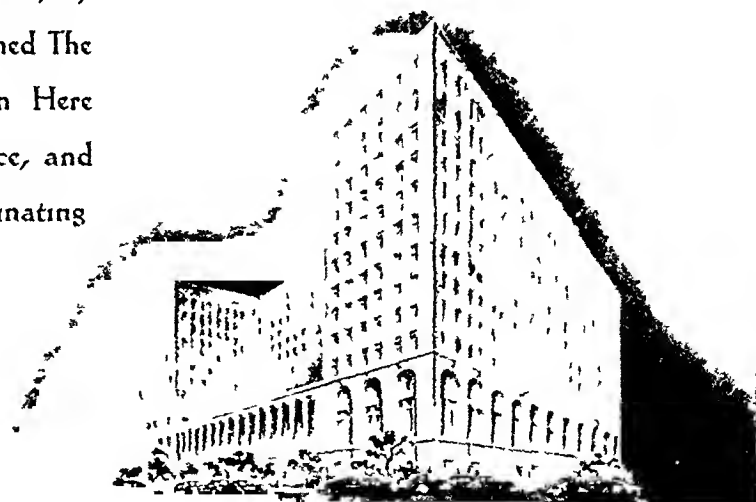
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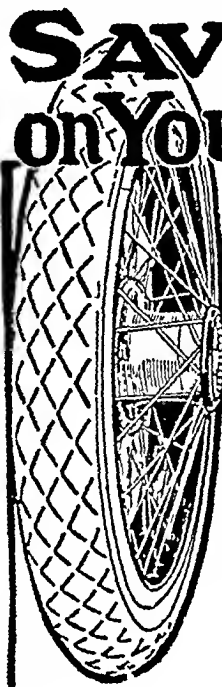
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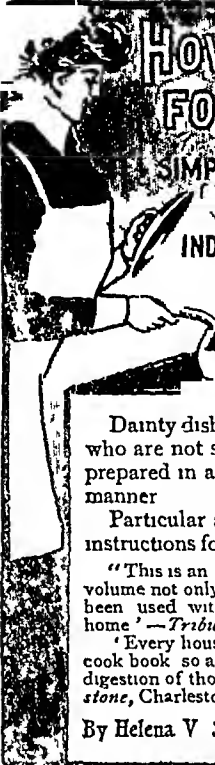
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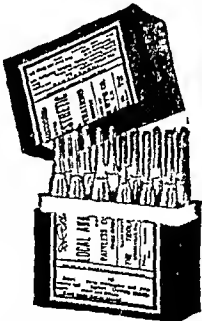
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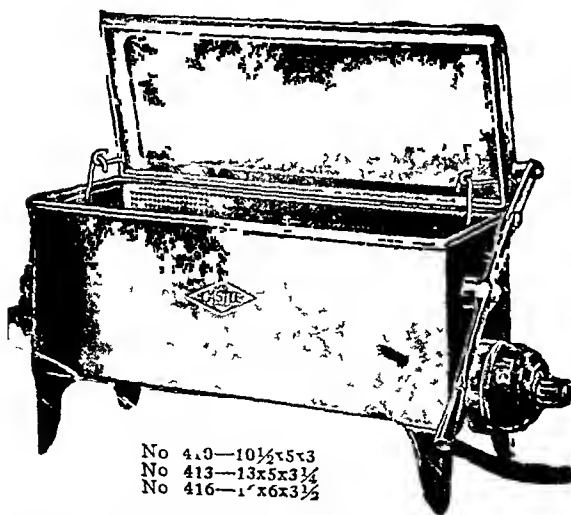
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